APPROACHES TOWARD THE SYNTHESIS OF THE SKELETAL CORE OF CYATHANE TYPE DITERPENES

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2003

This document is dedicated to Allen Sielert for making me realize that there is no dark side of the moon!

ACKNOWLEDGMENTS

I would first like to thank my mom, sister and grandparents for their unconditional love, understanding and support throughout my journey in life. Family should be the major influence in anyone's life and they have taught me many valuable lessons, and for that I am eternally grateful.

Next I would like to thank my advisor Dr. Dennis Wright for his guidance and more importantly his methods as a teacher. He is always willing to lend an ear and offer vast amounts of knowledge to just about any situation. I would also like to thank Dr. Merle Battiste, and Dr. Tomas Hudlicky for their many discussions about chemistry and life in general. They made learning about chemistry exciting and made my experience an enjoyable one. Dr. David Powell and Dr. Charles Allen are great committee members and we should all be so lucky. Thanks go to Dr. Jon Stewart for being a great co-advisor on our joint project. I also thank Dr. Eric Enholm for letting me begin my graduate studies at UF and letting me leave the group to join Dr. Wright's group with no ill feelings.

I would also like to thank the Wright group members. C-Nice, Ivar, Baker, Chris Whitehead, Lynn Usher, Maria Estrella and the rookie Jeff Sperry all made life in the lab bearable and somewhat enjoyable. Thanks go to Mike Green who worked for me as an undergraduate and I wish him the best in his endeavors. Brian Kyte also deserves thanks for his assistance in the yeast reductions and also for his input on this document.

Outside of chemistry there a lot of friends to thank because without their encouragement and friendship I would not be the person I am. I would first like to thank all my good ole' boys from home for countless memories and stories. Tommy Osborne, Bryan and Dave VanHoven, Andy Babcock and Cedric Bodway these guys are just about as good as it gets. Special thanks go to Cedric for all the summer work outs between football seasons. Playing football in college has impacted my life in ways I would have never imagined and the friendships that were forged are forever cherished. Thanks go to Blaze for being my twin brother (the ugly one) and always being there for me and also to big money Gil and his family for showing me that things really are bigger in Texas. Blake Perry is responsible for pushing me to do the best in school and pushing me down a mountain. Our late night study sessions and all around insanity in the science building can never be forgotten. I would also like to thank Tim Funderburk and his family for being my family while I was attending Greenville College. Upon my arrival to UF, Claude Robotham was the first person that I met and from our first experience at the Ale House to our escapades in Jacksonville he has been a valuable friend and roommate and thanks go to Todd Huml my other roommate for all trouble we would get into. I would also like to thank Chad Harrell for pulling me away from work long enough to remain sane and for reassuring me that I really stink at golf. Emily Gibb is responsible for keeping me focused on my goals and she is always there for me when I need her and for that I am thankful.

Finally I would like to thank my undergraduate professor Dr. Daryl Cox for getting me interested in organic chemistry and making me realize that there was more to life than football!

TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS iii

ABSTRACT viii

CHAPTER

1 BACKGROUND AND INTRODUCTION 1

- Chirality in Organic Synthesis 1
- The Synthesis of Highly Functionalized Seven Member Rings 2
  - Seven-Membered Rings from Acyclic Compounds and Ring Size Alteration 5
  - Cycloaddition Routes to Seven-Membered Ring Synthesis 8
- Conclusions 14

2 ASYMMETRIC REDUCTIONS OF 1, 3-DIKETONES TO BETA-KETO ALCOHOLS 16

- Asymmetric Chemical Reductions 16
  - Hydride Reductions 17
  - Transition Metal Catalyzed Reductions 21
  - Reductions of 1, 3-Diketones with Baker's Yeast 24
  - Acyclic 1, 3-diketones 25
  - Cyclic 1, 3-Diketones 27
  - Conclusions 27

3 CYATHANE TYPE DITERPENES 29

- The Cyathins 29
- The Erinacines 30
- The Scabronines and Sarcodonins 31
- Biosynthesis of the Cythane Core 32
- Biological Activity 33
- Total Syntheses 34
- Snider's Synthesis of Allocyathin B_2 and Erinacine A 34
- Tori's Synthesis of Allocyathin B_2 37
- Piers' Synthesis of (±) Sarcodonin G 40
- Conclusions 42

4 PROGRESS TOWARD THE SKELETEAL CORE OF THE CYATHANE TYPE DITERPENES 43

The Robinson Annulation Approach 43
Baker's Yeast Reductions of 3, 3-Disubstitiuted-Oxa-Bicyclo[3.2.1]Oct-6-Ene-2, 4-Diones 51
Access to the Cyathane Core through the Wieland-Miescher Ketone 61
Conclusions 64

5 EXPERIMENTAL 65

General Procedures 65
Two step procedure for tetrachlorocyclopropene[61] (185) 67
2,3,4,4-Tetrachloro-8-oxa-bicyclo[3.2.1]octa-2, 6-diene[12] (186) 68
3-Chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione[12] (187) 68
3-Chloro-3-(3-oxo-butyl)-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (188) 69
7-Chloro-12-oxa-tricyclo[7.2.1.$0^{2,7}$]dodeca-2, 10-diene-4, 8-dione (189ab) 70
3-Chloro-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2,4-dione (192a) 71
3-Allyl-3-chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (192b) 71
3-Benzyl-3-chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (192c) 72
3-Methyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (193) 73
3-Methyl-3-(3-oxo-butyl)-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (194) 73
7-Methyl-12-oxa-tricyclo[7.2.1.$0^{2,7}$]dodeca-2, 10-diene-4, 8-dione (195ab) 74
7-Methyl-12-oxa-tricyclo[7.2.1.$0^{2,7}$]dodecane-4, 8-dione (199) 75
General procedure for reductions using Baker's yeast[62] 75
3-Chloro-4-hydroxy-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (215a) 76
3-Allyl-4-hydroxy-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (215b) 77
3-Benzyl-4-hydroxy-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (215b) 77
4-Bromo-benzoic acid 3-chloro-3-methyl-4-oxo-8-oxa-bicyclo[3.2.1]oct-6-en-yl ester (214) 78
3,3-Dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (218) 79
Wieland-Miesher mono-ketal (223)[63] 79
6-Hydroxy-1, 1-(1, 2-ethylenedioxy)-8a-methyl-octahydro-naphthalene (224)[64]80
6-Benzyloxy-1, 1-(1, 2-ethylenedioxy)-8a-methyl-octahydro-naphthalene (225)81
6-Benzyloxy-8a-methyl-octahydro-naphthalen-1-one (226) 82
(6-Benzyloxy-8a-methyl-3, 4, 4a, 5, 6, 7, 8, 8a-octahydro-naphthalen-1-yloxy)-trimethyl-silane (227) 83

APPENDIX: SELECTED SPECTRA 84
LIST OF REFERENCES 121
BIOGRAPHICAL SKETCH 126

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

APPROACHES TOWARD THE SYNTHESIS OF THE SKELETAL CORE OF CYATHANE TYPE DITERPENES

By

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December 2003

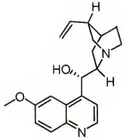
Chair: Dennis Wright
Major Department: Chemistry

Manipulations of 3-chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-diketones have been examined for use in natural product synthesis. Many of the cyathane class of natural products have been shown to stimulate the production of nerve growth factor (NGF) *in vivo*. Investigations toward the synthesis of skeletal core of cyathane type diterpenes, specifically the *trans*-fused 6, 7-ring system, have been attempted by Robinson annulations. Attempts to produce this desired ring system have also been researched by a ring expansion methodology on derivatives of the Wieland-Miesher ketone. The asymmetric reduction of 3-alkyl-3-chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-diketones by Baker's yeast has also been studied in order to produce chiral building blocks that can be used for natural product synthesis.

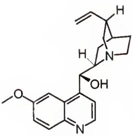
CHAPTER 1
BACKGROUND AND INTRODUCTION

Chirality in Organic Synthesis

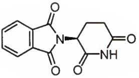
The synthesis of chiral drug molecules is at the forefront of modern day organic synthesis. Chirality can play an important role in drug synthesis because it is a prominent feature of most biological processes. It is well known that enantiomers of bioactive molecules often produce different biological effects. This is usually not a problem when dealing with compounds that are isolated and used from natural sources. They are obtained in pure form as a single enantiomer. The problem arises when these molecules are produced by chemical processes. These compounds can be mixtures of a number of stereoisomers depending on how many chiral centers are contained in the molecule. For the synthetic chemist, these mixtures are still useful; the problem arises if these compounds are to be used for therapeutic purposes. It is now known that different stereoisomers of a molecule can have significant effects on pharmacological action (Figure 1-1). The effects of both isomers can be helpful such as with quinidine (antiarrythmic) and quinine (antimalarial). A classic example of tragic effects of a racemic drug is illustrated with thalidomide. This drug was marketed in the 1960's as a sedative and administered as a racemate. At that time it was not known that while the R-enantiomer was an effective sedative, the S-enantiomer was teratogenic and caused fetal anomalies.[1] The drug ketamine is another example of racemates possessing



quinidine
(antiarrythmic)
1

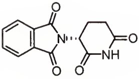


quinine
(antimalarial)
2

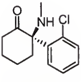


teratogen
3

thalidomide

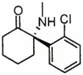


sedative
4



anaesthetic
5

ketamine



hallucinogen
6

Figure 1-1. Examples of drugs where chirality affects result

undesirable side effects; the R-enantiomer is a hallucinogen and the S-enantiomer is an active anesthetic and analgesic.[2] The stereoisomeric composition of drug substances has rapidly become an important issue in the development, approval and clinical use of pharmaceutical preparations. Accordingly, drug regulatory authorities have adopted strict policies to develop drugs only in their single stereoisomer forms to ensure optimal efficacy and avoid unwanted side-effects.[3]

The Synthesis of Highly Functionalized Seven Member Rings

The synthesis of chiral, highly functionalized five and six member rings has been well investigated in the literature over the years. However, methods to achieve the seven member moiety have been rather limited. There are a number of natural products that contain a chiral seven member ring and several of these are under investigation for therapeutic applications (Figure 1-2).

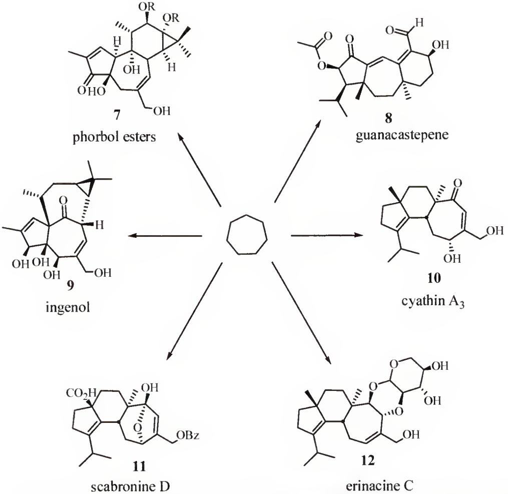


Figure 1-2. Natural products with highly functionalized seven-membered rings

The structural complexity of these selected examples shows the importance of extending the methodologies available to produce seven member rings. The synthesis of any ring system can be categorized in one of four strategic classes (Figure 1-3): closure of an acyclic precursor, ring size alteration (expansion or contraction), fragmentation, and cycloaddition.[4] Acyclic closures involve the formation of a new bond. The starting

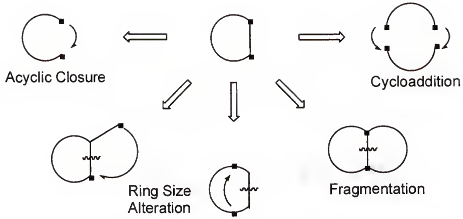
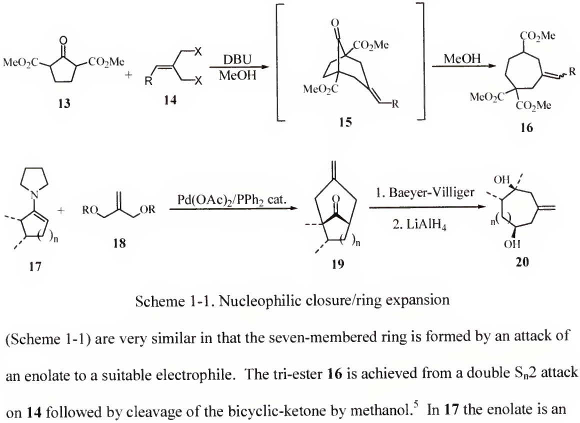


Figure 1-3. Strategies for ring formation

materials are usually simple molecules that when linked together form the ring. This increases the complexity of the system, which is the goal of organic synthesis: to use simple starting materials to form complex molecules in the fewest number of steps. In the case of ring size alteration a new bond is also made but one is lost as well. These types of transformation can occur as a single operation or in series. In these reactions the complexity of the target molecule is not necessarily greater than that of the starting materials; because of this the synthesis of the starting materials may be just as difficult as the target ring. Products of fragmentation reactions are usually less complex than the starting materials as well. This type of transformation is a great asset, especially when the precursors are readily available and when the product is a macrocycle. The cycloaddition reaction is a very powerful tool for increasing molecular complexity; it relies on simple starting materials; it forms two bonds at once and it is a method of synthetic convergence.

Seven-Membered Rings from Acyclic Compounds and Ring Size Alteration

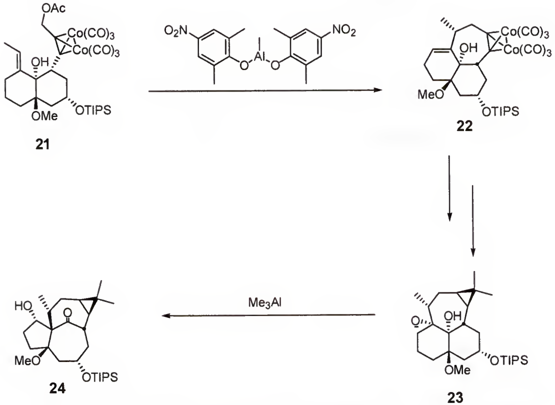
When forming rings from acyclic precursors, there are two ways to approach the synthesis, either by an intermolecular or intramolecular reaction. In the case of intermolecular reactions, if the desired ring is a five or six-membered ring, then the laws of thermodynamics will aid in the formation of the ring. However, in the case of larger membered rings, entropic factors are problematic because there are more degrees of freedom associated with the ring formation. Usually very high dilution and long reaction times are employed to produce the product in low yield. This problem is circumvented by doing the reactions in an intramolecular fashion. Most of the successful examples in the literature are accomplished by this method. The two approaches illustrated (Scheme 1-1) are very similar in that the seven-membered ring is formed by an attack of an enolate to a suitable electrophile. The tri-ester **16** is achieved from a double S_n2 attack on **14** followed by cleavage of the bicyclic-ketone by methanol.[5] In **17** the enolate is an enamine which can be readily made from many cyclic ketones. The enamine is nucleophilic enough to attack **18** after the palladium has coordinated with the OR group.



Scheme 1-1. Nucleophilic closure/ring expansion

The cleavage of the bridged ketone is achieved in a two-step process by a Baeyer-Villiger oxidation of the bridged ester **19** followed by reduction with lithium aluminum hydride to afford the seven-membered ring diol **20**.[6]

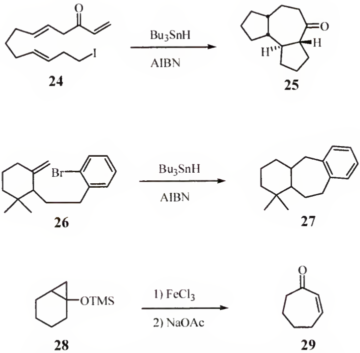
Attack of an electrophile is another way to facilitate the formation of a seven-membered ring. This type of reaction is usually assisted by a Lewis acid in order to generate a cation. Kuwajima and co-workers[7] have developed a novel two step process for the synthesis of the highly strained ingenane skeleton (Scheme 1-2). The first step employs a Nicholas cyclization of the cobalt complex **21**. Treatment of **21** with methylaluminum bis(2, 6-dimethyl-4-nitrophenoxide) affords the allyl alcohol **22** and the seven-membered C-ring of ingenol. In a series of steps the cobalt complex is removed by a Birch reduction, followed by installation of the gem-dimethylcyclopropane, and finally



Scheme 1-2. Electrophilic closure/rearrangement in the total synthesis of ingenol

a stereospecific epoxidation of the allyl alcohol gives **23**. Under the influence of trimethylaluminum a Pinacol-type rearrangement occurs with a ring expansion/contraction of the fused decalin system, which yields the complete ABCD-ring system of ingenol.

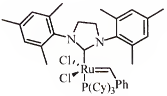
The use of radicals has proven to be a very versatile way of achieving cyclization. Radicals can create rings from acyclic precursors or they can initiate a ring expansion/contraction. Pattenden et al.[8] demonstrated that tricycle **25** can be produced with, tribuyltin hydride. The tin abstracts an iodine radical, which then undergoes a 13-*endo*-trig closure to produce the initial macrocycle; then two subsequent 5-*exo*-trig transannulation processes gives tricycle **25**. Ghatak et al.[9] have also shown that 7-*endo*-aryl radical cyclizations are possible with tribuyltin hydride to afford aryl tricycle **27**. Seven-membered enones have been generated from the corresponding TMS-cyclopropyl



Scheme 1-3. Seven-membered rings from radicals

ethers from a radical accelerated ring expansion, which produces an initial *β*-chloro ketone. Upon reflux in a sodium acetate solution, enone **29** is generated.[10]

In the past couple of years, ring closing methathesis (RCM) has been used to synthesize rings of various sizes. The popularity of this method has increased due to generation of more reactive, yet stable catalysts. RCM reactions are initiated by a carbene or carbenoid which is complexed with a metal. The most popular of these reagents is the Grubbs' catalyst **30**. Krafft and co-workers[11] used RCM to generate the 5-5-7 tricycle **32**.



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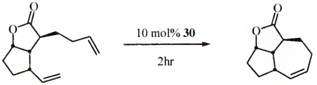
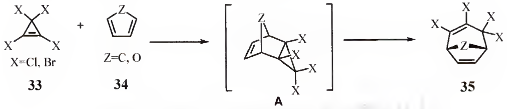


31 **32**

Scheme 1-4. RCM with Grubbs' catalyst

Cycloaddition Routes to Seven-Membered Ring Synthesis

Arguably, the most famous of all name reaction is the Diels-Alder reaction. The Diels-Alder reaction is a [4+2] cycloaddition and refers to a reaction of a 4_{pi}-electron diene with a 2_{pi}-electron dieneophile to generate a six-membered ring. This reaction has been widely used to construct, in a region- and stero-controlled way, six-membered rings with up to four sterogenic centers and it is a frequently used method to produce a wide range of complex molecules. However, its use for the production of seven-membered rings has been very limited. Tobey and Law[12] demonstrated that the bicyclic seven-membered ring **35**, could be formed from a reaction of furan or cyclopentadiene with the desired tetrahalocyclopropene. The intermediate **A** is formed from the initial Diels-Alder reaction, which then spontaneously rearranges to relieve the ring strain of the cyclopropane. The bond migration followed by trapping of the resultant cation by the halogen is believed to be a concerted process. This example shows the power of the convergent nature of cycloaddition reactions. From the relative simplicity of the starting materials, **35** is produced which has all of the carbons functionalized.



Scheme 1-5. [4+2] cycloaddition/rearrangement

In order to expand the scope of a (4_{pi}+2_{pi}) cycloaddition other reactions have been

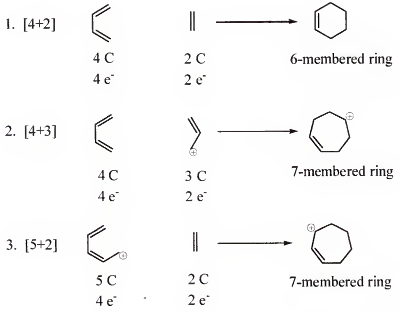
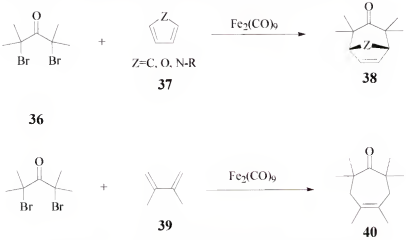


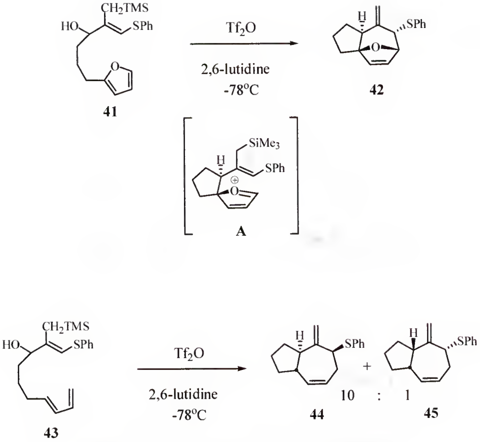
Figure 1-4. Cycloadditions isoelectronic with the classic Diels-Alder reaction

developed which are not of the classic Diels-Alder type. These reactions still include a 4_{pi}-electron diene and a 2_{pi}-electron dieneophile but the notation is based on the number of atoms in each component of the cycloaddition (Figure 1-4).[13] The annotation of brackets will now refer to the number of atoms involved in the cycloaddition. The [4+3] cycloaddition involves the use of an allyl cation. Usually the cation is generated by the use of a α, α'-dihalo ketone, which upon removal of the halogen, generates the reactive oxy-allyl cation species. Noyori et al.[14] showed that the reactive oxy-allyl cation species



Scheme 1-6. [4+3] oxy-allyl cation cycloaddition

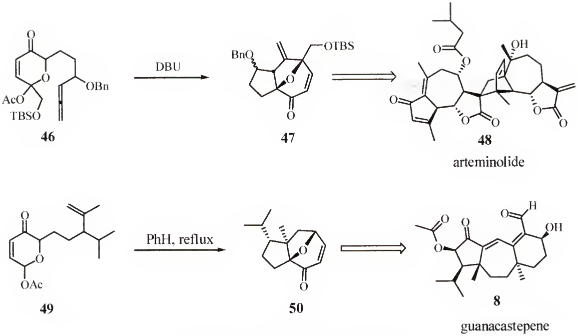
could be produced from the use of diiron nonacarbonyl and a α, α'-dihalo ketone. They demonstrated that bicyclic and monocyclic seven-membered rings could be produced in relatively good yields. The use of the oxy-allyl cation is limited because it can only be generated from α, α'-dihalo ketones, so it has only been used in an intermolecular fashion. However, there are other ways of generating the allyl cation species. Harmata and co-workers[15] used an allylic alcohol to generate the allyl cation (Scheme 1-7). The alcohol **41** reacts with triflic anhydride and then is displaced by electron flow from the sulfur, which generates the allyic cation. The diene then closes to form the five-membered ring first leading to intermediate **A**, followed by the closure of the seven-



Scheme 1-7. Intramolecular [4+3] cycloaddition

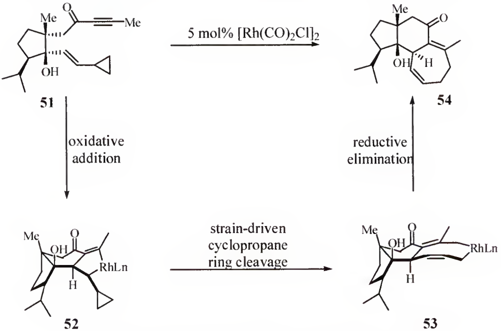
membered ring. This produces a tertiary cation, which upon work-up gives the final bicyclic product **42**. Harmata also showed that the diene is not limited to a cyclic species; however, mixtures of the resultant cycloadduct were observed **44** and **45**.

Another type of cycloaddition is the [5+2] cycloaddition. These types of reactions usually involve oxidopyrylium or oxidopyridinium ions, as the 5-atom source, attached to an alkene, alkyne or allene. In his approach to the total synthesis of arteminolide, Lee et al.[16] combined an oxidopyrylium ion with an allene in order to generate **47** with the exo-methylene. This reaction produced a 2:1 mixture of cycloadducts that could be separated. Magnus et al.[17] adopted a similar strategy in his pursuit of the total synthesis of guanacastepene. Their efforts resulted in a 95:5 ratio of cycloadducts that could be separated, with the major product as **50**. As shown the [5+2]



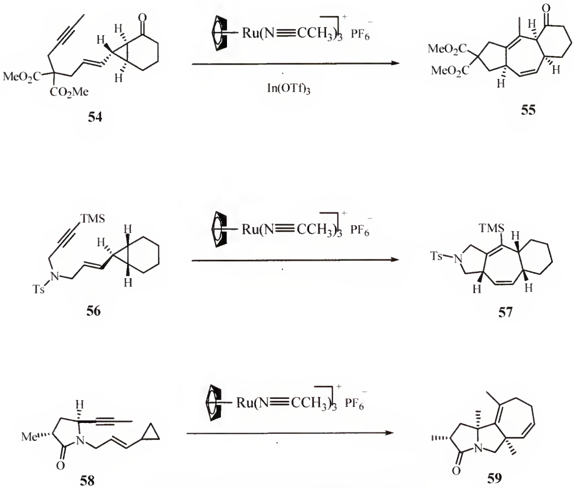
Scheme 1-8. [5+2] cycloadditions

cycloaddition can be a very easy way to quickly generate complex molecules from fairly simple precursors. The disadvantage of this methodology is that it is limited by the requirement that the oxidopyrylium or oxidopyridinium ions serve as the reactive 5-atom



Scheme 1-9. Wender's approach to the cyathane core

unit. In the mid-1990's Wender and co-workers[18] demonstrated that by using a rhodium catalyst ($RhCl(PPh_3)_3$) the 5-atom component of the [5+2] cycloaddition could come from a vinylcyclopropane derivative. Wender used this tool to elegantly synthesize (+)-dictamnol[19] but recently applied this methodology toward the synthesis of the 5-6-7 tricyclic core of the cyathane type diterpenes,[20] which will be discussed later in this document (Scheme 1-9). Trost and Shen[21] also used the [5+2] cycloaddition to produce

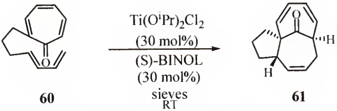


Scheme 1-10. [5+2] applications by Trost

the 5-7-6 tricyclic core **55** of such natural products as phorbol and guanacastepene. He also demonstrated that non-basic nitrogens, which are incorporated into the vinylcyclopropane tether, could be used to give access to azapolyhydroazulenes such as

57 (Scheme 1-10). In another application, lactam **58** was used to generate the 5-5-7 tricycle **59**.

The last of the high order cycloaddition reactions to be examined is the [6+4] cycloaddition. This reaction has been known for some years and usually involves a reaction between a tropone derivative and cyclopentadiene along with a protic acid catalyst.[22] These reactions give good yields but require elevated temperatures that can exceed 80°C which, combined with the acid catalyst does not tolerate a wide variety of functional groups. Rigby and Fleming[23] have developed a simple yet effective solution for this problem. In his approach to the total synthesis of ingenol he adopts the use of a Lewis-acid mediated [6+4] cycloaddition (Scheme 1-11). It was found that 25 mol% of $FeCl_3$ lead to the cycloadduct at room temperature. The product, however, was a mixture of isomers. In light of this a chiral Lewis acid was examined which gave **61** in an 80% yield and in 40% enatiomeric excess (ee) at room temperature.



Scheme 1-11. [6+4] cycloadditions

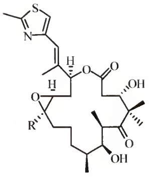
Conclusions

Over the years great progress has been made in the synthesis of seven-membered rings. An overview of the various approaches toward the synthesis of seven-membered rings was provided and is by no means exhaustive. The choice of appropriate methodology is based on the target molecule. With this array of methods already discovered and those not yet investigated, further research can only add to the scope of organic synthesis.

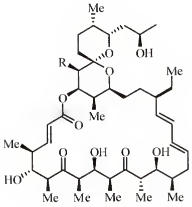
CHAPTER 2
ASYMMETRIC REDUCTIONS OF 1, 3-DIKETONES TO BETA-KETO ALCOHOLS

Asymmetric Chemical Reductions

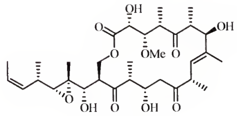
As many natural products exist as a single stereoisomer, asymmetric synthesis is required to chemically prepare identical material. Prior to 1970, few asymmetric reactions were known that provided high enantiomeric excess (ee). Over the past ten years there has been an explosion of new methods and techniques that yield optically active compounds.[24] The bulk of these methods involve the use of transition metal catalysts or metal hydride reagents to facilitate the reactions. The asymmetric reduction of carbonyl compounds has been one of the areas most affected by the use of transition metal catalysts and metal hydride reagents. The ability to produce chiral alcohols in high enantiomeric excess has given rise to a vast array of chiral building blocks as well as natural products. Many methods exist for the asymmetric reduction of carbonyl compounds,[25] such as *β*-keto esters and simple ketones, but there are only a handful for 1, 3-diketones. The asymmetric reductions of 1, 3-diketones is an easy way to obtain optically active *β*-keto alcohols, which often appear in various natural products (Figure 2-1). This type of functionality can also constitute a particularly versatile class of chiral building blocks since a variety of further chemical derivatizations are possible. For example, further reduction of the chiral *β*-keto alcohols can give rise to *syn*- and *anti*-1, 3 diols, which are recurring units in a variety of polyacetate- and polypropionate-derived natural products.[26]



epothilone A (R = H)
epothilone B (R = Me)



rutamycin B (R = H)
oligomycin C (R = Me)

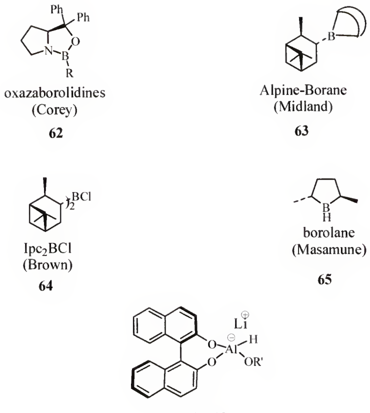


tedanolide

Figure 2-1. Natural products containing *β*-keto alcohols

Hydride Reductions

The asymmetric reductions of symmetrical and unsymmetrical mono-ketones by hydride reagents are well represented in literature.[25] To be considered an asymmetric reduction, a single enantiomer must be produced with selectivity (> 90% ee). To achieve the delivery of hydride selectively to one face of prochiral ketones, lithium aluminum hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$), and borane-tetrahydrofuran complex (BH_3-THF) reagents have been modified with optically active ligands.[27] Selected reagents for the enantioselective reduction of ketones are illustrated (Figure 2-2), only one enantiomer is shown. Although these reagents have shown great success in the asymmetric reduction of mono-ketones, their applications to 1, 3-diketones (in route to



oxazaborolidines
(Corey)
62

Alpine-Borane
(Midland)
63

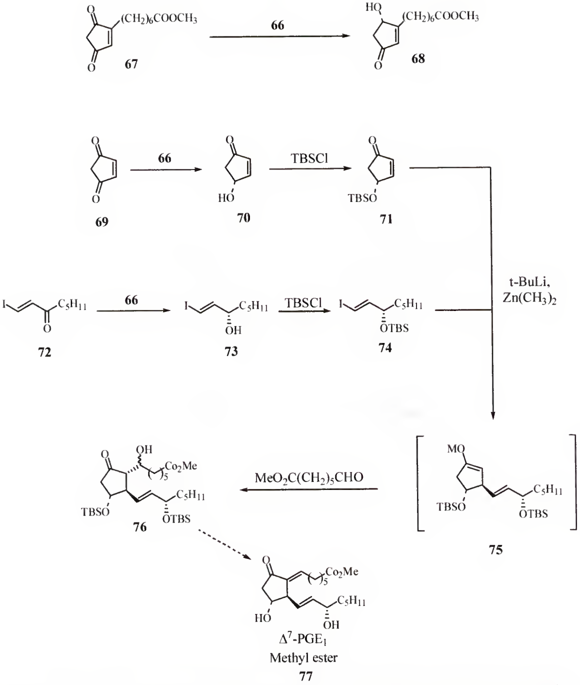
Ipc$_2$BCl
(Brown)
64

borolane
(Masamune)
65

BINAL-H
(Noyori)
66

Figure 2-2. Optically active ligands for asymmetric reduction of ketones

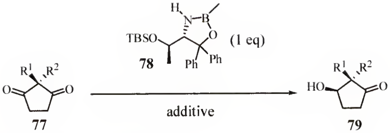
β-keto alcohols) has been very limited. Attempts to achieve mono-reductions usually have failed because the reagents are very reactive toward ketones, which results in production of 1, 3-diols. Even though the 1, 3-diol functionality can be applied to a number of natural products, methods to produce the chiral intermediate from mono-reduction remained elusive. Noyori and co-workers[28] were the first to successfully use metal hydrides to produce β-keto alcohols in high yields and in high enantiomeric excess (Scheme 2-1). By using the binaphthol-modified lithium aluminum hydride reagent **66** they were able to convert the 1, 3-diketone **67** into the corresponding β-keto alcohol **68** in 76% yield in 91% ee. With these results, they applied their methodology toward a short, enantioselective total synthesis of Δ^7-PGE$_1$ methyl ester, **77**. In a very unique and



Scheme 2-1. Noyori's approach to prostaglandins *via* chiral aluminum hydride reduction

elegant application they use **66** to afford both chiral synthons for a convergent route. The meso 1, 3-diketone **69** is converted to the single enantiomer **70,** with a 94% ee, and the resultant alcohol is protected to give synthon **71**. To produce the second precursor, they show the scope of their modified aluminum hydride reagent by selectively reducing the simple ketone **72** to the single stereoisomer **73**, with a 97% ee. Protection of the alcohol with TBSCl affords **74**. The two pieces are then connected through a dimethyl zinc assisted 1, 4-addition of the vinyl anion of **74** to enone **71**. The enolate is then trapped through an aldol reaction with methyl 6-formylhexanoate to give **76**. Dehydration of the aldol product followed by deprotection of the alcohols gives Δ^7-PGE$_1$ methyl ester **77**.[29] Although the results of Noyori's work with metal hydrides are impressive the main drawback to his methodology is that the chiral hydride reagent must be used in excess with respect to the diketone because the reagent has only one hydride to react. This quickly becomes a very expensive reagent because of the chiral ligand that is required to achieve high enantioselectivity.

Shimizu et al.[30] was the first to show that a borane reagent could be used to mono-reduce a 1, 3-diketone in a stereocontrolled fashion (Table 2-1). His work involved the use of a BH$_3$-oxazaborolidine derived from *L*-threonine to achieve the formation of either 1, 3-diols or *β*-hydroxy ketones by choosing the approiate reduction conditions. The reductions were carried out in a variety of conditions and it was found that the addition of N, N-diethylaniline to the reaction gives the desired mono-reduction product in moderate yields with high enantioselectivity. The addition of the amine serves two roles, control of enantioselectivity of the first reduction and the suppression of the second one. Currently, no further explanations of these results have been offered but they are under further investigation by his group.



77a: R^1= Me, R^2= Bn **77b**: R^1= R^2= Me

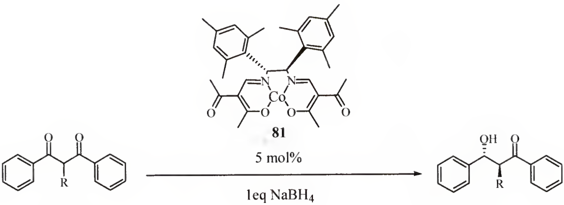
77c:R^1= R^2= Bn **77d**: R^1= Me, R^2= allyl

77	Additive (equiv)	BH_3-THF (equiv)	Time (hr)	Yield (%)	ee
77a	N, N-Diethylaniline (0.5)	2.0	1	44	94
77b	N, N-Diethylaniline (2.0)	4.0	19	40	96
77c	N, N-Diethylaniline (0.5)	2.0	19	71	88
77d	N, N-Diethylaniline (0.75)	3.0	19	63	90

Table 2-1. Mono-reduction of 1, 3-cyclopentadione to β-hydroxy ketone

Transition Metal Catalyzed Reductions

Until recently, the use of transition metals for reductions has been limited to β-keto esters. This work, which was pioneered by Noyori and Ohkuma,[31] involved the use of hydrogen and $[Ru(BiNAP)Cl_2](NEt_3)$ as the catalyst. Applications of this method to other substrates have been scarce and limited to a few cyclic imides[32] and diamides.[33] In a series of papers, Yamada has demonstrated that the chiral β-ketoiminato cobalt complex **81** could be used in combination with $NaBH_4$ to produce α-alkyl-β-keto alcohols in high enantioselectivity. The interpretation of this work can be somewhat skewed depending on what kind of 2-alkyl-1, 3-diketone is being reduced. In the first of his papers he demonstrated that if a symmetrical 2-alkyl-1,3-diketone is used then high yields of the corresponding *anti*-products are obtained with high enantioselectivity (Table 2-2).[34] It can be seen that very high ee's are obtained with a very high percentage of



81

5 mol%

1eq $NaBH_4$

80

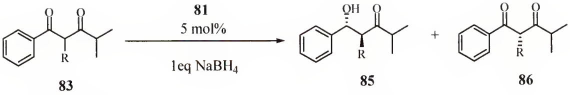
82

80a: R= Me
80b: R= allyl
80c: R= benzyl

1, 3 Diketone	Yield (%)	*anti*-selectivity	ee (%)
80a	93	99	99
80b	88	98	97
80c	96	99	98

Table 2-2. Cobalt catalyzed reduction of symmetrical 1,3-diketones

conversion. The explanation given for the enantioselectivity of this reaction is that the cobalt hydride species formed attacks only one face of the ketone, based on the Felkin-Anh model. These results have been extensively studied in the cobalt-catalyzed borohydride reduction of mono-aryl ketones.[35] In his next paper, Yamada applied his methodology to the reduction of unsymmetrical ketones.[36] He finds that when reductions are attempted a chiral resolution is obtained which gives the *anti-β*-keto alcohol and the now chiral unreacted 2-alkyl-1, 3-diketone. Because this reaction is a chiral resolution, the maximum amount that can be obtained of each product is 50%. This is in contrast to the *meso*-2-alkyl-1, 3-diketones, which upon reduction are able to yield a maximum of 100% conversion. Despite of this, the enantioselectivity of the reduction is very high and the *chemo*-selectivity of the reaction is excellent (Table 2-3). The reduction is



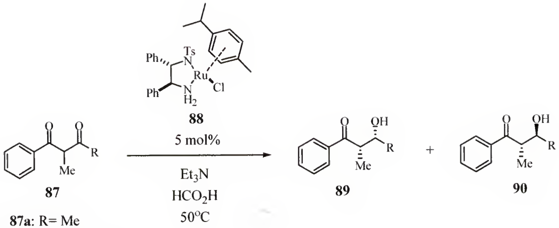
83a: R= Me
83b: R= Et
83c: R= allyl

1,3-Diketone	Yield/conv. (%)	*chemo*-select/%	*anit*-select/%	ee/%
83a	46/48	99	99	96
83b	41/42	99	99	98
83c	47/48	95	98	96

Table 2-3. Cobalt catalyzed reduction of unsymmetrical 1, 3-diketones

completely selective to the aryl ketone, which occurs because the cobalt-catalyzed borohydride reduction of mono-aryl ketones is known to proceed very fast.[37] Investigations are underway by Yamada to expand the scope of this methodology to alkyl-1,3-diketones.

Cossy et al.[38] has developed a ruthenium based catalyst for the reduction of 2-alkyl-1, 3-diketones. The methodology developed by Cossy compliments the work of Yamada in that the reduction is also enantioselective but the major product is the *syn-β*-keto alcohol instead of the *anti*-product. The reduction uses (S, S)-RuCl[N-(tosyl)-1, 2-diphenylethylenediamine](*p*-cymene) **88** as the reduction catalyst and achieves dynamic kinetic resolution (Table 2-4). This reduction achieves a dynamic kinetic resolution because of the conditions in which it is run. The elevated temperature along with the presence of formic acid allows for the epimerization of the α-methyl. This drives the reduction to give impressive diastereomeric ratios of **89** to **90** and high enantioselectivity



87a: R= Me
87b: R= $(CH_2)_2CH{=}CH_2$
87c: R= CH_2NHCBz
87d: $(CH_2)_2NHBoc$

	Yield (%)		ratio		
1,3-diketone	**89** + **90**	convn (%)	**89**/**90**	**89** ee (%)	**90** ee (%)
87a	84	96	92/8	96	-
87b	87	89	91/9	98	-
87c	81	100	83/17	89	84
87d	88	100	97/3	97	80

Table 2-4. Ruthenium catalyzed reduction of 2-alkyl-1, 3-diketones

of each. However, Cossy later describes that as the steric hindrance of the R group increases on the ketone, both diastereo- and enantioselectivity decrease significantly along with increase in reaction times.

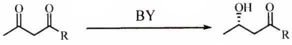
Reductions of 1, 3-Diketones with Baker's Yeast

The properties of *Saccharomyces cerevisiae* or Baker's yeast (BY) as a reducing agent have been known since it was first observed by Dumas in 1874. In his investigations he determined that upon the addition of finely powdered sulfur to a fermenting yeast suspension in a sugar solution, hydrogen sulfide was given off.[39] Since that initial discovery, BY as well as other microbes, and purified enzymes have been used for reductions of a variety of organic compounds. The asymmetric reduction of carbonyl-containing compounds by BY constitutes one of the most widely applicable reactions. The main advantage of using living organisms or purified enzymes as reagents is that, by nature, they are selective for whatever task they are required to do. This usually leads to high distereo- and enantioselectivity from the reactions. For the purposes of this document the discussion will be limited to the use of only BY for the reductions of 1, 3-diketones.

Acyclic 1, 3-diketones

The use of BY for the reduction of 3, 3'-unsubstituted-2, 4-diones was studied extensively by Ohta and co-workers.[40] Their results showed a direct correlation of the yield of the *β*-keto alcohol to the length of the alkyl chain attached to the ketone. Since BY reactions are done in water this shows that the more non-polar you make a substrate the less likely it will find its' way into the cell to be reduced (Table 2-5). Even though the yields drop off substantially as the alkyl chain grows, the enantioselectivity remains excellent and the chemoselectivity remains constant through each example, in that, only the methyl ketone is reduced. When the alkyl chains are extended on both ketones the amount of conversion to product drops drastically and the mixtures of products are only obtained if the 1, 3-diketone reactant is unsymmetrical. The ee's remain acceptable for each compound. They also reported that bis-reduction is not apparent and that recovery of the 1, 3-diketone is possible.

In addition to the *α*, *α'*-unsubstitiuted-2, 4-diones, mono- and di-substituted examples have been investigated. For the 3-methyl-branched compound **93** an

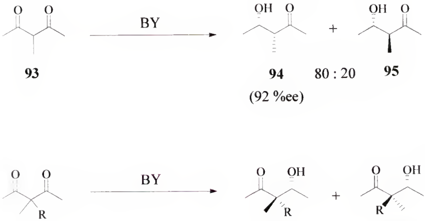


91 **92**

R	time (d)	yield (%)	ee (%)
CH_3	6	90	>99
C_2H_5	3	100	>99
n-C_3H_7	2	62	94
n-C_4H_9	2	42	>99
n-C_5H_{11}	2	25	96
n-C_8H_{17}	2	23	97

Table 2-5. Baker's yeast reduction of 2, 4-diones

80:20 mixture of the *syn*- and *anti*-*β*-keto alcohol isomers are isolated in a 30% yield with a 92% ee of the major *syn*-product (Scheme 2-2).[41] This result suggests that there is a high enantiofacial selectivity in the reduction of the pro-chiral carbonyl groups, but low



93 **94** 80 : 20 **95**

(92 %ee)

96 **97** **98**

96a: R= allyl
96b: R= $CH_2C(CH_3)$=CH_2

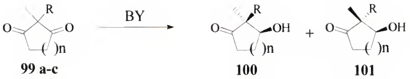
Scheme 2-2. Reduction of *α*-substituted 1, 3-diketones diastereofacial selectivity since both (3R)- and (3S)-methyl ketols were obtained. In the reduction of α, α'-substitiuted-2, 4-diones, low yields were also obtained in mixtures of diastereomeric ketols of **97a/b** and **98a/b**. The ee's remain high for the major *syn*-product **98a/b**, in excess of >98% for each.[42]

Cyclic 1, 3-Diketones

The use of BY for the reduction of various cyclic 1,3-diketones has been extensively studied by Brooks and co-workers.[43] They demonstrated that BY could be used to reduce 5-, 6-, 7-, 8-, and 9-membered rings that contain 1,3-diketones (Table 2-6). They claim that in all reactions attempted the ee of the major product was >98% and, in most cases, excellent diastereomeric ratios were also obtained. As shown by the table, the size of the ring directly affects the yield of the reaction. This occurs because the reactions are run in an aqueous media and the more non-polar or hydrophobic you make a substrate the less likely it is to find its' way into the cell to be reduced. Although the yields are very poor in the larger ring experiments, the ee's remain very high for the major product.

Conclusions

Asymmetric reductions have proven to be a valuable tool for the production of chiral alcohols for use as reactive intermediates or as building blocks. In light of the relatively few methods available for the production of β-keto alcohols from 1,3-diketones, novel methodologies must be examined to expand the scope of these reactions.



entry	R	de **100:101** (%)	yield (%)	ee
99a (n= 1)	propyl	100:0	60	<98
99b (n= 1)	allyl	90:10	75	<98
99c (n= 1)	propargyl	67:33	60	<98
99d (n= 2)	propyl	22:78	80	<98
99e (n= 2)	allyl	45:55	80	<98
99f (n= 2)	propargyl	27:73	75	<98
99g (n= 3)	propyl	2:98	10	<98
99h (n= 3)	allyl	100:0	20	<98
99i (n= 3)	propargyl	71:29	60	<98
99j (n= 4)	allyl	82:18	5	<98
99k (n= 5)	allyl	no product	0	0

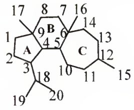
Table 2-6. Reduction of α,α'-dialkyl-cyclic-1, 3-diketones with Bakers' yeast

CHAPTER 3
CYATHANE TYPE DITERPENES

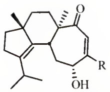
Cyathins were first isolated in the early 1970's by Ayer and co-workers from the fungus *Cyathus helenae*. Attention was first given to the cyathins because of their antibiotic activity toward Gram positive and Gram negative bacteria as well as actinomycetes.[44] However, synthetic investigations were not pursued until the early 1990's when Kawagishi et al.[45] isolated the analogous erinacines from *Hericium erinaceum* and the scabronines[46] and sarcodonins[47] from *Sarcondon scabrosus*. These newly isolated analogs of the cyathins have been shown to be potent stimulators of nerve growth factor (NGF) *in vitro.*[45-47] It is for this reason that several attempts toward their synthesis are underway. These compounds have been separated into three general classes of compounds that contain the cyathane core.

The Cyathins

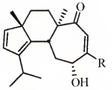
The parent class are the cyathins (Figure 3-1), which are diterpenoid in nature and thus a nomenclature system was devised based primarily on the degree of unsaturation present in the compound.[44] Isolated C-20 compounds with 30 hydrogen atoms were classified as cyathin A derivatives, 28 hydrogens as cyathin B derivatives and those with 26 hydrogens as member of the cyathin C class. The subscript after the letter refers the number of oxygen atoms present in the molecule. For example, cyathin A_3 (**101**) has 30 hydrogens and 3 oxygen atoms. When a structural isomer of a known cyathin was isolated it was given the prefix *allo*. All of the cyathins share the same base skeletal



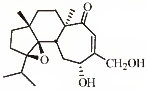
cyathane numbering system



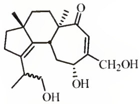
102 cyathin A_3 (R=CH_2OH)
103 cyathin B_3 (R=CHO)



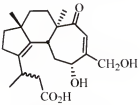
104 allocyathin B_3 (R=CH_2OH)
105 cyathin C_3 (R=CHO)



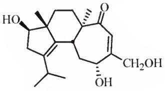
106 neoallocyathin A_4



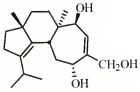
107 cyathin A_4



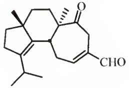
108 cyathin C_5



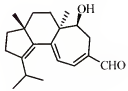
109 cyafrin A_4



110 cyathatriol



111 cyathin B_2



112 allocyathin B_2

Figure 3-1. Structures of the cyathin diterpenes

structure in that they all possess a twenty-carbon skeleton arranged in a 5-6-7 fused tricyclic core, with the fused 6-7-ring junction being trans (the carbons are numbered as shown in Figure 3-1). There are also two angular methyl's located at C-9 and C-6 in a trans orientation with respect to each other, and finally, there is an isopropyl group located at C-3.

The Erinacines

The erinacines are a related family of the cyathins in that they also possess the same inner skeletal structure known as the cyathane core. These compounds were first isolated by Kawagishi and co-workers[45] from the mycelia of the fungus Hericium erinaceum and were to be known as erinacines A-F (Figure 3-2). These molecules are basically a D-xylose moiety linked to the cyathane skeleton. The absolute configurations have been determined Kawagishi and co-workers for all compounds except erinacine F 118.

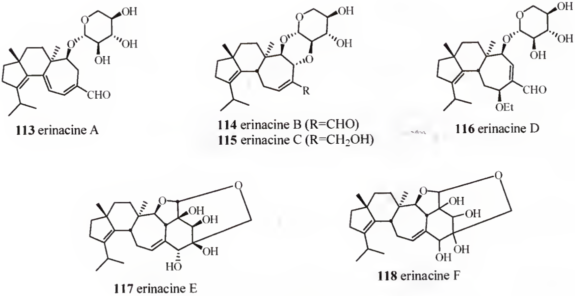
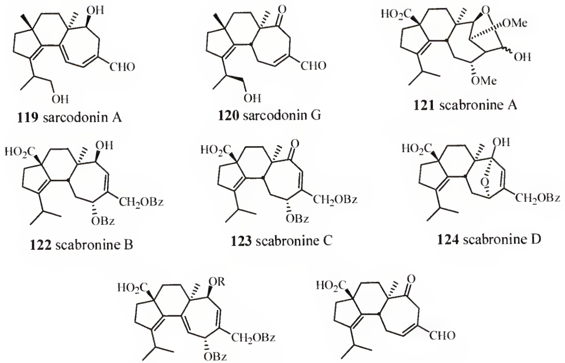


Figure 3-2. Structures of the erinacines

The Scabronines and Sarcodonins

The sarcodonins A-H were the first of the two families to be isolated by Hirota and co-workers[47] from the mushroom *Sarcodon scabrosus*. To date, only the structures of sarcodonin A (**119**) and G (**120**) have been determined. Ohta and co-workers[46] isolated five other cyathane type derivatives known as the scabronines A-G (**121-127**). The major difference between these compounds and the parent cyathins is the oxidation state of C-20 on the isopropyl group in the sarcodonins and the C-17 methyl in the scabronins.

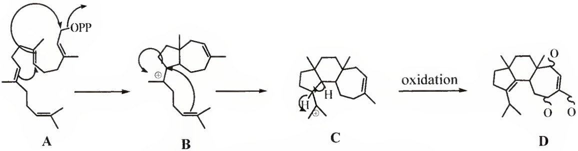


119 sarcodonin A
120 sarcodonin G
121 scabronine A
122 scabronine B
123 scabronine C
124 scabronine D
125 scabronine E (R=Ac)
126 scabronine F (R=H)
127 scabronine G

Figure 3-3. Structures of the scabronines and sarcodonins

Biosynthesis of the Cythane Core

When Ayer and co-workers first isolated the cyathins, they investigated their base core biosynthesis through ^{13}C labeling experiments.[48] They hypothesized that since the cyathane core is diterpenoid in nature; it should arrive from geranylgeranyl pyrophosphate, which serves as the acyclic C-20 precursor. Upon feeding the fungus *C. earlei* ^{13}C-labled acetate and analyzing the resultant ^{13}C spectrum of the product cyathatriol (**110**), they determined that the synthesis must go through the pathway illustrated above (Scheme 3-1). The proposed synthesis involves an initial cationic closure, with loss of the phosphate from the geranylgeranyl pyrophosphate (**A**) to give a fused 5-7-ring junction. A subsequent Wagner-Meerwein rearrangement gives the ring expanded fused 6-7 system, followed by a cationic closure of the five-membered ring to



Scheme 3-1. Proposed cyathane biosynthesis

complete the fused 5-6-7 tricyclic ring core (**C**). Elimination and a 1, 2-hydride shift onto the isopropyl cation followed by a few oxidation steps leads to (**D**).

Biological Activity

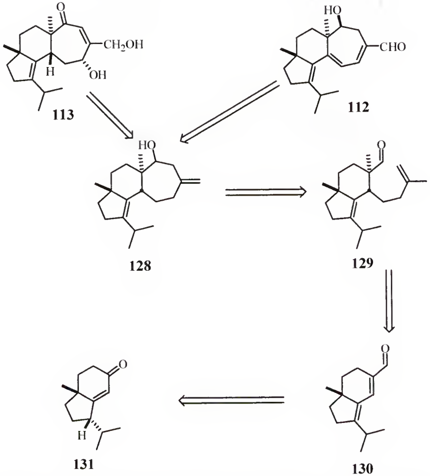
Upon initial isolation of the cyathins by Ayer, it was discovered that several of the compounds had antibiotic activity against Gram positive and Gram negative bacteria as well as actinomycetes.[44] The interest in these molecules lay dormant until the discovery of the erinacines and scabronines. These newly found classes of cyathane type diterpenes were shown to stimulate the biosynthesis of nerve growth factor (NGF) and other neurotrophic agents.[45, 46, 49, 50] These agents were sought for the treatment of a number of neurodegenerative disorders based on the encouraging results *in vitro*.[51] However, the use of NGF in clinical trials have failed because of its' unfortunate pharmacological characteristics.[52] It lacks the ability to pass through the blood-brain barrier (BBB) and administration of the drug is done by direct injection into the cerebral spinal fluid (CSF).[52, 53] This produces numerous clinical problems, so attention was directed toward other means of using NGF as a therapeutic agent. Since NGF is produced naturally by the body, efforts were turned to regulating its' production *in vivo*. The erinacines and scabronines are just a few of the newly discovered molecules envisioned for this purpose.

Total Syntheses

To date, there have been only three groups that have successfully synthesized one or more of the cyathanes. Two of the routes deal with allocyathin B_2 **112,** which does not contain the *trans*-fused 6, 7 ring system and the other synthesis is of sarcodonin G (**120**). Erinacine A **113** has also been synthesized through the use of **112.**

Snider's Synthesis of Allocyathin B_2 and Erinacine A

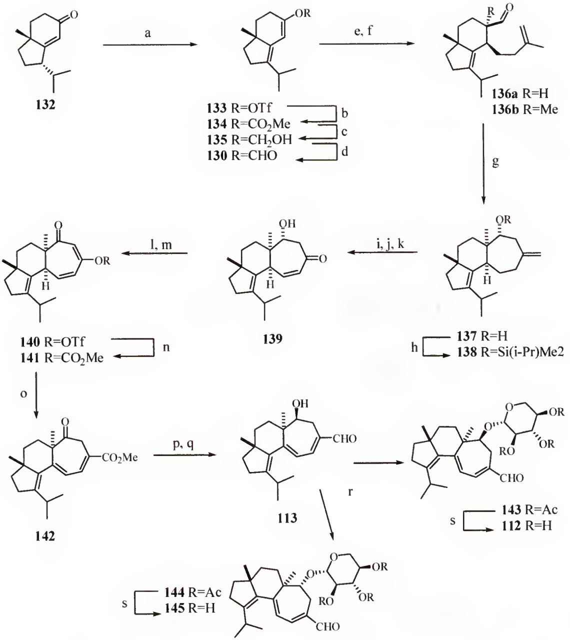
Snider et al.[55] were the first to complete a total synthesis of the cyathane type diterpenes. The initial compound that was synthesized was (±) **112**, which were converted into (+) **113** by glycosidation. In the retrosynthetic analysis, Snider envisioned



Scheme 3-2. Snider's retrosynthesis of allocyathin B_2 and erinacine A

the closure of the C-ring of the cyathane skeleton *via* a carbonyl ene reaction to give intermediate **128** which can be converted into both desired natural products (Scheme 3-2.) The synthesis of enantiopure **131** was completed by Snider and has proven to be a valuable and easy method for access to the cyathane skeleton.

Their total synthesis starts by γ-deprotonation of enone **132** and trapping of the enolate as a vinyl triflate. The vinyl triflate **133** is converted into aldehyde **130** in a series of steps that involves a palladium catalyzed coupling of **133** with carbon monoxide in methanol. This results in the production of methyl ester **134**, which is reduced to the corresponding primary alcohol. Oxidation of the alcohol with manganese dioxide gives **130**. The homo-allylic side chain was introduced by a 1, 4-addition of isopentenylmagnesium bromide catalyzed by copper bromide. This reaction was accelerated by the addition of TMSCl and gave **136a** as a 4:6 mixture of isomers at C-6. Along with this result, the stereochemistry at C-5 from the cuprate addition was found to be opposite of the saturated 6, 7-ring junction that occurs in the natural products. However, this was irrelevant because **112** and **113** contain sp^2 carbons at C-5. Installation of the angular methyl at C6 was accomplished by alkylation of **136a** with a large excess of methyl iodide and potassium t-butoxide. This resulted in a 15:1 mixture of *α*-methylated aldehyde **136b**. The stereochemistry of the major isomer from the alkylation was later determined to be that shown by **136b**. The tri-cyclic skeleton of the cyathane core was then closed by a carbonyl-ene reaction to produce alcohol **137** in high yield and as a single isomer. The alcohol was then protected and the *exo*-double bond was oxidativily cleaved and the resultant ketone converted into the *β*-hydroxy enone **139** with phenylselenium chloride and hydrogen peroxide followed by alcohol deprotection. The



(a) Proton Sponge, Tf_2O, 88%; (b) $Pd(OAc)_2$, Ph_3P, CO, i-Pr_2EtN, MeOH, 85%; (c) DIBAL, 97%; (d) MnO_2, 95%; (e) $H_2CC(CH_3)(CH_2)_2MgBr$, CuBrDMS, TMSCl, 91%; (f) KO-t-Bu, MeI, 75%; (g) Me_2AlCl, 87%; (h) i-$Pr(Me)_2SiCl$, imid., 95%; (i) OsO_4, KIO_4, 77%; (j) LHMDS, PhSeCl, H_2O_2, 72%; (k) AcOH, H_2O; (l) Dess-Martin, 72% from **140**; (m) KHMDS, $PhNTf_2$, 75%, (n) $Pd(OAc)_2$, Ph_3P, CO, i-Pr_2EtN, 75%; (o) Et_3N, MeOH, 94%; (p) LAH, 89%; (q) MnO_2, 94%; (r) triacetyl-a-D-xylopyranosyl bromide, $Hg(CN)_2$, HgCl, 34%; (s) K_2CO_3, MeOH, >90%.

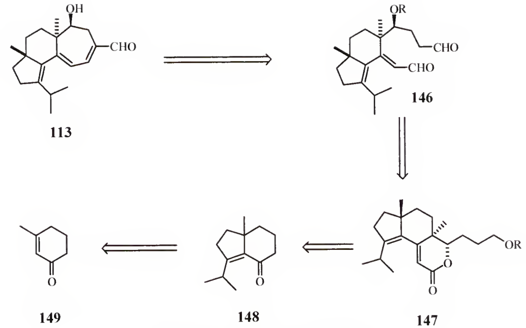
Scheme 3-3. Snider's approach to allocyathin B_2 and erinacine A

β-hydroxy enone **139** was then oxidized to the corresponding 1, 3-diketone, which was selectively converted to the vinyl triflate **140**. Again, a palladium-catalyzed carbonylation was used (in methanol) to convert the vinyl triflate **140** to the β–keto methyl ester **141**. Treatment of β-keto ester with triethyl amine in methanol afforded the conjugated trienoate **142**. Total reduction of all carbonyls followed by selective oxidation of the primary alcohol yielded (±) **113**. Glycosidation of (±) **113** with 2, 3, 4-tri-O-acetyl-α-D-xylopyranosyl bromide gave an easily separable 1:1 mixture of **143** to **144** with recovery of starting material. After removal of the acetates, the spectral data was identical to that of naturally occurring **112**. Snider achieves **113** in 17 steps and **112** in 19 steps.

Tori's Synthesis of Allocyathin B_2

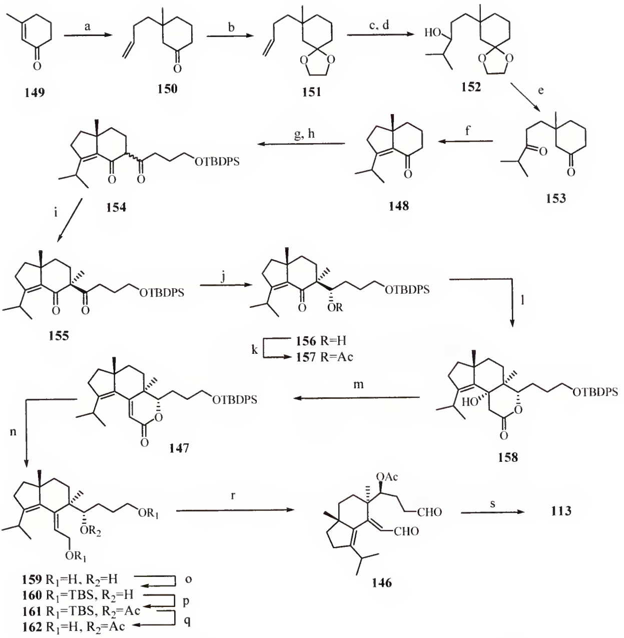
Tori and co-workers[56] have also completed the synthesis of **113** and by doing so has also achieved a formal synthesis of **112** *via* Snider's work. The synthetic strategy envisioned involved the use of three key aldol condensation reactions. One of these reactions was used to close the C ring of the cyathane skeleton and install the C-11, C-12 double bond **146** (Scheme 3-4). In order to obtain the C-5, C-10 double bond an intramolecular aldol condensation was utilized to generate lactone **147**. The stereochemistry at C-6 of **147** could be controlled by the order of alkylation of **148**. Finally, hydrindanone **148** was derived from another intramolecular aldol condensation of functionalized **149**.

Tori begins his synthesis with the readily available 3-methylcyclohexenone **149** and sets the quaternary center of C-9 with a 1,4-conjugate addition of 4-bromo-1-butene catalyzed by Copper (I) bromide (Scheme 3-5). The ketone is then protected as a ketal



Scheme 3-4. Tori's retrosynthesis

and the double bond is subjected to ozonolysis followed by a reductive work-up. Isopropylmagnesium bromide is added to the resultant aldehyde to arrive at **152**. The alcohol is then oxidized under Jones conditions, which in turn, hydrolyzes the ketal and affords di-ketone **153**. The first of three aldol reactions is then performed to arrive at the fused 5, 6 A-B ring system of the cyathane core **148**. The next step is to set the correct stereochemistry of C-6, and this was achieved by the correct addition of alkylating agents. Through a set of experiments they found that incoming electrophiles will add *anti* to the C-9 methyl. This allowed the addition of the side chain first, in the form of an enolate acylation, followed by introduction of the methyl group with methyl iodide. This nicely sets the *anti* relationship between the two methyl groups in **155**. After screening different reduction conditions it was found that zinc borohydride gave correct diastereomer **156** as the major product, with a ratio of 15:1 and a yield of 50%. The mixture of alcohols was converted into their corresponding acetates and were then separated by silica gel chromatography. With the correct stereoisomer in hand, an



(a) $CH_2CHCH_2CH_2MgBr$, $CuBr/Me_2S$; (b) $HOCH_2CH_2OH$, p-TsOH, PhH, 99% from **149**; (c) O_3, Zn, HOAc; (d) *i*-PrMgBr, 83%; (e) Jones oxidation; (f) 5% KOH/MeOH, 73% from **152**; (g) LDA, $ClCO(CH_2)_3OTBDPS$, -78°C; (h) 5% KOH/MeOH, 37%; (i) *t*-BuOK, MeI, 91%; (j) $Zn(BH_4)_2$, -78°C, 50%, (k) Ac_2O, DMAP, Py, 98%; (l) LHMDS, -78°C, 80%; (m) $SOCl_2$, Py, 0°C, 50%; (n) LAH; (o) TBSCl, Et_3N, 37% from **147**; (p) Ac_2O, DMAP, Py; (q) PPTS, MeOH, 52% from **160**; (r) Swern oxidation; (s) 5% KOH/MeOH, 74% from **162**.

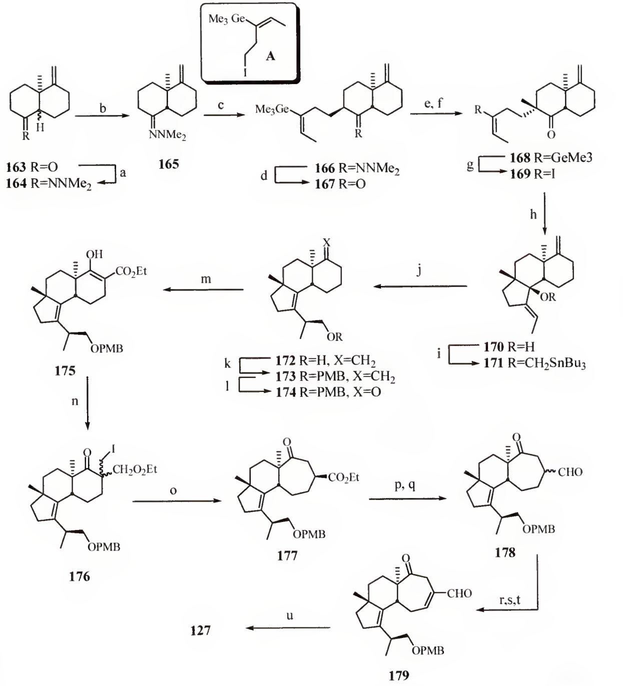
Scheme 3-5. Tori's synthesis of allocyathin B_2

intramolecular aldol reaction was performed to give lactone **158**. Dehydration of **158** to the α, β- lactone, gave **147** as the major isomer, the minor isomer could be isomerized to **147** under basic conditions. Reduction of the lactone with LAH followed by protecting group alterations gave the diol **162**. Oxidation of both primary alcohols to aldehydes set the stage for the final aldol cyclization to close the C-ring and subsequent deprotection of the C-14 alcohol gave **113** in 18 steps.

Piers' Synthesis of (±) Sarcodonin G

Piers and co-workers[57] were the first to attempt a synthesis of a molecule from the sarcodonin family. Specifically, the target molecule was sarcodonin G **127**. The choice of the target differs from the previously discussed compounds in that in addition to the *trans*-angular methyls, it also has a *trans*-fused 6, 7-ring system (the B and C rings). In addition **127** also possess a functionalized *iso*-propyl group. It contains a hydroxyl group at C-19 which in turn renders C-18 a stereogenic center.

The synthesis begins with the known mixture of bicyclic ketones **163**. Upon treatment of **163** with dimethylhydrazone, **164** was obtained as a mixture of *cis*-, *trans*-isomers in a 1:1 ratio. After separation, acid-catalyzed equilibration of the *cis*-isomer converts most of the material to **165.** Taking advantage of Tori's work, the side-chain **A**, (which was obtained in 6 steps from ethyl pent-2-ynoate) was introduced first and the methyl second after hydrolysis of the hydrazone. This set the *trans*-relationship between the angular methyl at C-6 and the newly installed methyl at C-9 in **168**. Removal of the trimethylgermane was facilitated by *N*-iodosuccinimide to afford the vinyl iodide **169.** Lithium halogen exchange of the vinyl iodide lead to smooth formation of the 5, 6, 6-fused ring system as a single isomer. Installation of the functionalized *iso*-propyl group



(a) Me$_2$NNH$_2$, CSA, 82%; (b) CSA, PhH, reflux; (c) KDA, DMPU, **A**; (d) HOAc, NaOAc, 69% from **164**; (e) NaOMe, MeOH, 82%; LiNEt$_2$, CH$_3$I, 85%; (g) NIS, 90%; (h) BuLi, 86%; (i) KH, 18-C-6, Bu$_3$SnCH$_2$I; (j) BuLi, 88% from **170**; (k) KH, PMBCl, TBAI, 96%; (l) OsO$_4$, KIO$_4$, 85%; (m) KH, NaH, (EtO)$_2$CO, 74%; (n) TBAF, Ch$_2$I$_2$, 78%; (o) SmI$_2$, 71%; (p) DIBAlH; (q) Dess-Martin periodinane, 86% for two steps; (r) piperidine, PhH, PhSeCl; (s) KIO$_4$, 78% for two steps; (t) DBN, PhH, 95%; (u) DDQ, H$_2$O, 91%

Scheme 3-6. Piers' synthesis of (±)-sarcodonin G was accomplished by conversion of the tertiary alcohol to the corresponding stannane derivative **171**. Subjecting **171** to *n*-butyl lithium triggered a [2, 3]-sigmatropic rearrangement, which yielded **172** with the correct stereochemistry at C-18. Having installed all of the necessary stereogenic centers, attention was diverted toward completing the cyathane skeleton. Protection of the newly installed alcohol as a *p*-methoxybenzyl ether (PMB) followed by chemoselective oxidative cleavage of the *exo*-methylene produces ketone **174**. Acylation of ketone **174** with diethylcarbonate provided enol ester **175**, which, upon treatment with tetrabutylammonium fluoride (TBAF) in the presence of diiodomethane afforded **176** as a mixture of isomers. Exposure of the isomers to samarium diiodide facilitated a one carbon ring expansion to the seven-membered ring **177** as a single isomer. Exhaustive reduction of **177**, followed by oxidation, gave the keto aldehyde **178** as a mixture of epimers. Conversion of the aldehyde to the corresponding enanime, followed by addition of phenylselenenyl chloride, yielded the corresponding selenide as a mixture of epimers. Oxidation-elimination of the selenide provided a mixture of positional isomers, which upon isomerization under basic conditions afforded only **179**. Finally, removal of the PMB protecting group gave (±) **127** in 21 steps from **163**.

Conclusions

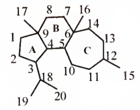
To date there have only been three total syntheses of any members of the cyathane family. With the exciting biological activity of this family of compounds it is only a matter of time before more discoveries will be made.

CHAPTER 4
PROGRESS TOWARD THE SKELETEAL CORE OF THE CYATHANE TYPE DITERPENES

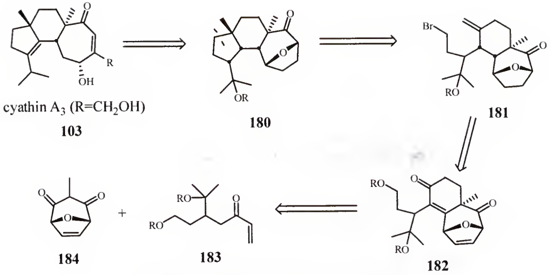
As described in the previous chapter, the cyathane type diterpenes are an exciting class of natural products because of their biological activity and structural complexity. Our group has already addressed one approach toward the cyathane skeleton[58], this discussion will illustrate two alternative approaches of this synthetic methodology.

The Robinson Annulation Approach

In the three approaches that lead to the total synthesis of one or more of the cyathanes, the C-ring was installed last. We envisioned starting with a functionalized seven-membered ring and building the rest of the molecule on to it. We selected **102** (cyathin A_3) as our target molecule (Scheme 4-1). The key features of the molecule are the C-6 and C-9 angular methyls and the *trans*-fused B and C rings. It can be seen that **180** is a precursor of **102** without specific functionality around the 7-membered ring. We hoped to take advantage of the biosynthetic pathway to put the molecule together. If a cation were generated at C-18, an elimination of a proton on C-3 could be induced followed by a 1, 2-hydride shift, just as in the proposed biosynthesis. Observing the structure **180**, if a disconnection is made between C-1 and C-9 then **181** would arise. A radical closure of the five-member ring would give the *cis*-adduct if the hydrogen at C4 was up. It can be envisioned that hydrogenation of **182** would be *exo* due to the assistance of the oxo-bridged bicyclic system thus leading to **181**. Compound **182** can



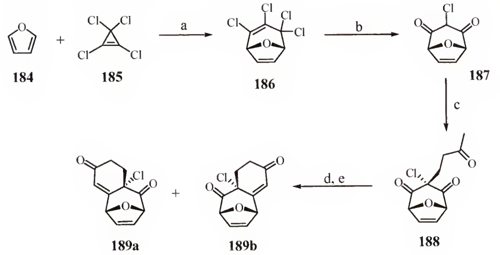
cyathane numbering system



Scheme 4-1. Retrosynthesis of cyathin A$_3$

be envisioned from a Robinson annulation of **183** with **184**. The stereochemistry of the C-6 center should be controlled by the exo-alkylation of the Michael addition.

Based on our retrosynthetic plan, a model study was initiated based on the work of Toby and co-workers.[12] They synthesize **187** from a Diels-Alder reaction between **184** and **185**, which upon spontaneous rearrangement of the initial adduct, affords **186** (Scheme 4-2). Subjecting **186** to concentrated sulfuric acid for 10 min, yields **187** in moderate to low yields. It was at this point that we investigated a Robinson annulation of **188**. Standard conditions were explored for the Michael addition such as sodium hydroxide and potassium hydroxide. These strong alkoxide bases did not give any of the desired product **188**, but only destruction of the starting material. These observations lead us to believe that **187**, although very acid stable, was sensitive to the alkoxide bases. We then moved toward amine bases and triethylamine was our first choice, it was chosen because of the suspected low pk$_a$ of the hydrogen α- to the chlorine. These conditions proved to be successful and product **188** was obtained in good yield. When **188** was isolated we speculated that the stereochemistry of the alkylation proceeded through an *exo*-addition which put the chlorine in the endo-position. Fortunately a crystal of **188** was obtained and based on X-ray analysis, it was determined that the chlorine was *endo* (Figure 4-1). With the stereochemistry defined we were in position to initiate the aldol condensation to close the six-membered ring. This was accomplished by using potassium *tert*-butoxide in THF. We hesitated to use KO*t*-Bu at first; having already established that the compound was sensitive to alkoxide bases, but it provided smooth conversion to



(a) CCl_4, 80°C sealed tube, 80%; (b) H_2SO_4, 90°C, 40%; (c) methyl vinyl ketone, Et_3N, THF, 75%; (d) potassium t-butoxide, THF; (e) p-TsOH, THF, 70%

Scheme 4-2. Model study results

the initial β-hydroxy ketone. Conversion of the initial aldol product to the enone was facilitated by acid catalyzed dehydration, to produce **189** as a racemate.

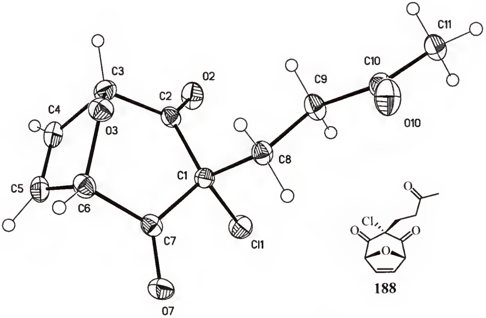
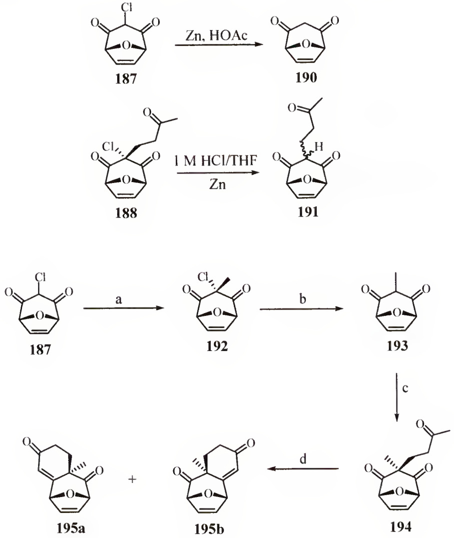


Figure 4-1. X-ray crystal structure of **188**

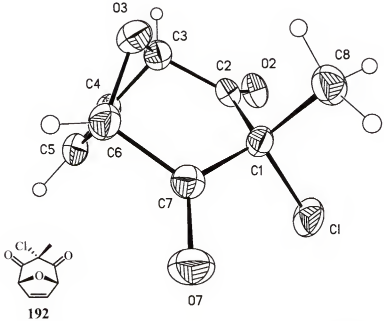
With the data obtained from the model study, we then focused on installing a methyl between the two ketones. The introduction of this methyl would correlate to the C-9 methyl in the cyathane skeleton and we were fairly confident that we could control the stereochemistry at that center by the proper order of alkylation. Initial investigations involved the reduction of the chlorine in **187** with zinc. We speculated that if a zinc enolate could be produced, such as in the Reformatsky reaction, then reduction of the chlorine and methylation could be done in one pot. Employing zinc dust or zinc/copper couple under anhydrous, oxygen free conditions did not reduce the chlorine. The only method that succeeded in removing the chlorine was with zinc dust in acetic acid as the solvent (Scheme 4-3). These conditions were effective for generating **190** completely by thin layer chromatography (TLC); however isolation of the product proved to be



(a) MeI, Et_3N, 70%; (b) Zn, 1M HCl, THF, 70-80%; (d) methyl vinyl ketone, Et_3N, 85%; (d) PhH, pyrrolidine, Dean-Stark trap, 80%.

Scheme 4-3. Zinc reduction optimization and synthesis of B-C ring precursor

problematic. Once the chlorine was removed, it was found that **190** was very water-soluble and could not be isolated by aqueous work-up. Furthermore, neutralization of the acetic acid was not possible because enolate formation of **190** occurred with the use of sodium bicarbonate. Attempts to remove the acetic acid *in vacuo* resulted in decomposition of the material. Conditions were worked out so that only 1.1 eq of acetic acid was necessary to reduce the chlorine. Isolation was also possible by aqueous work-up but neutralization of the acid was still not possible without destruction of **191**. It was then necessary to explore other routes to remove the chlorine. After considerable experimentation, a simple solution was achieved. The reduction of the chlorine could be achieved by adding 1M HCl drop-wise to a slurry of zinc dust in THF. Production of **191** occurred within seconds of adding a few drops of HCl, and the reaction was complete (by TLC) in a matter of minutes. Isolation by aqueous extraction gave **191** in good yield. This compound would prove to be insignificant because methylation of **191** would generate the opposite stereochemistry. Therefore, **187** was methylated with methyl iodide. Because methyl iodide is a small electrophile we wanted to make sure the

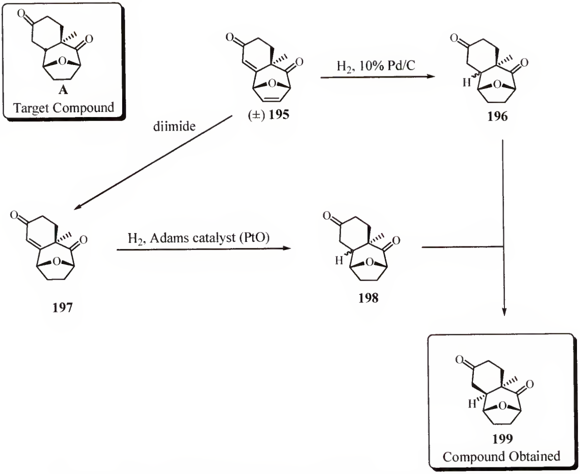


192

Figure 4-2. X-ray crystal structure of **192**

alkylation occurred exclusively from the *exo*-face. A crystal of **192** was obtained and demonstrated that the methylation occurred from the *exo*-face (Figure 4-2). The chlorine was then reduced by the optimized conditions of 1M HCl and zinc dust. Isolation of **193** was achieved by continuous extraction overnight to achieve good mass recovery. A Michael addition with MVK occurred smoothly just as before, to give trione **194**. Closure of the B-C rings was facilitated by a pyrrolidine catalyzed aldol condensation. This resulted in formation of **195a** and **195b** as a racemate with the correct relative stereochemistry at C-9. Having successfully achieved the Robinson annulation in a racemic fashion, efforts were turned toward investigating an asymmetric version of this reaction. Because the starting material is *meso* in nature, a single enantiomer could be produced if the appropriate catalyst was used. In the literature D- or L-proline has been shown to catalyze the Robinson annulation in a chiral fashion.[58] L-proline was chosen as the catalyst and after lengthy experimentation, it was determined that no suitable conditions could be found to achieve a useful degree of enantioselectivity. Reactions attempted at 0°C or below did exert some selectivity but the reaction times were in excess of one week, depending on the temperature and large amounts of starting trione were recovered.

In light of the unsuccessful attempts to achieve desired selectivity in the Robinson annulations, focus was then directed toward setting the *trans* relationship of the fused 6, 7 ring system. It was thought that global hydrogenation of (±) **195** would afford the desired stereochemistry (Scheme 4-4). The initial attempt with 10% palladium on charcoal gave **196** in high yield. Spectral analysis by 2D-NMR indicated that the delivery of hydrogen had occurred in a *syn* fashion with respect to the angular methyl at C-9. It was hypothesized that complexation of the *cis*-double bond to the catalyst facilitated delivery of hydrogen on the same side of the methyl. Removal of the *cis*-double bond in (±) **195** was achieved by reduction with diimide. The resultant α, β unsaturated ketone **197** was



Scheme 4-4. Attempts to set the *trans*-6, 7 ring system by hydrogenation

then reduced with Adams catalyst in the presence of hydrogen. The NMR data obtained from **198** was identical to that of **196**. To further support the data obtained, a crystal was acquired of **196** and submitted for X-ray analysis (Figure 4-3). The results from the X-ray analysis supported the assignments made by NMR, with the resultant saturated bicyclic system being *cis*-fused. With these disappointing results we decided to explore other methods in order to generate the desired ring system from **192**.

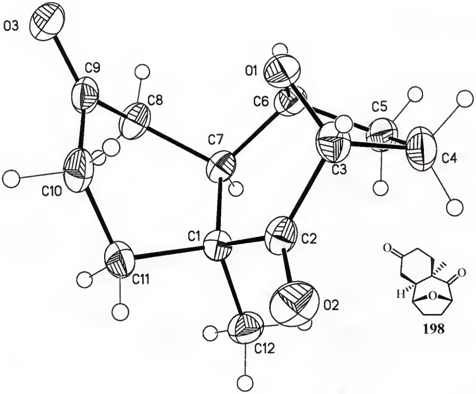
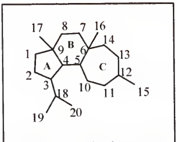


Figure 4-3. X-ray analysis of **198**

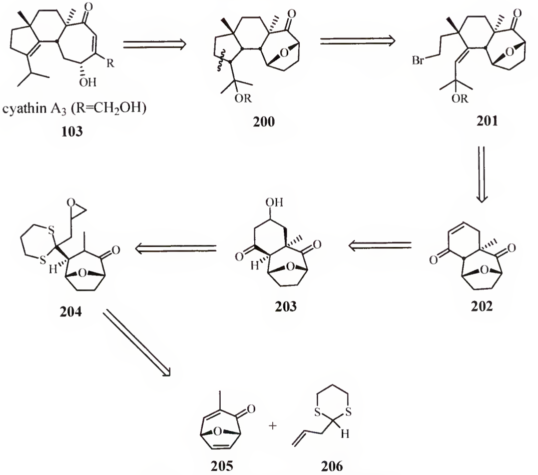
Baker's Yeast Reductions of 3, 3-Disubstitiuted-Oxa-Bicyclo[3.2.1]Oct-6-Ene-2, 4-Diones

This work was a cooperative project with Dr. Jon Stewart's group, specifically Brian Kyte. His contribution was optimization of the microbial reduction and conditions. My contribution to the project was synthesis and characterization of all materials chemically and characterization of all products obtained from the whole-cell yeast reductions.

In keeping with our initial synthetic strategy of building the seven-membered ring first, we redesigned our synthetic strategy (Scheme 4-5). In this route we again will try and take advantage of the proposed biosynthetic pathway of generating **103** from **200**.



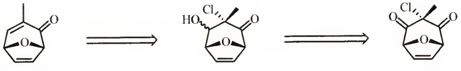
cyathane numbering system



Scheme 4-5. Retrosynthesis of cyathin A_3

We then envisioned the production of **200** from a radical closure of **201** which would generate the **A** ring with all of the newly installed hydrogens up. Compound **201** could arise from manipulation of enone **202**. Reduction of the double bond would give the corresponding saturated ketone as an intermediate of **201**. Then correct order of alkylation on the ketone should produce **201** with the indicated stereochemistry which would set the *trans* relationship of the two methyls at C-6 and C-9. The *trans*-fused 6, 7 ring system could be achieved from epimerization of β-keto alcohol **203**. Depending on the conditions used it should also be possible to facilitate the α, β-unsaturated ketone as well. Closure of the 6-membered **B** ring would result from nucleophillic opening of the epoxide by an enolate generated at C-6. Based on previous results, opening of the epoxide by the enolate should proceed in an *exo*-fashion producing β-keto alcohol **203** as a *cis*-fused system. The generation of **204** could occur from the derivatization of **205**. Reduction of the *cis*-double bond with diimide followed by conjugate addition of **206** should set the correct stereochemistry if the trend of *exo*-addition continued. Finally epoxidation of the terminal alkene would produce **204**. From this revised synthetic approach, it can be seen that the key intermediate would be the synthesis of enone **205** as a single enantiomer in order to approach the synthesis in an asymmetric fashion.

Based on previous work already discussed in this document, we decided to investigate the reduction of the novel 3-chloro-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione **192** by Baker's yeast (Scheme 4-6). Baker's yeast was selected for the



Scheme 4-6. Retrosynthesis of enone **205**

mono-reduction of the 1, 3-diketone because of its' broad substrate capacity, ease of use and usually high levels of enantioselectivity. Removal of the chlorine in the fermentation product **207** followed by subsequent elimination of the hydroxyl group would give the desired staring material **205**.

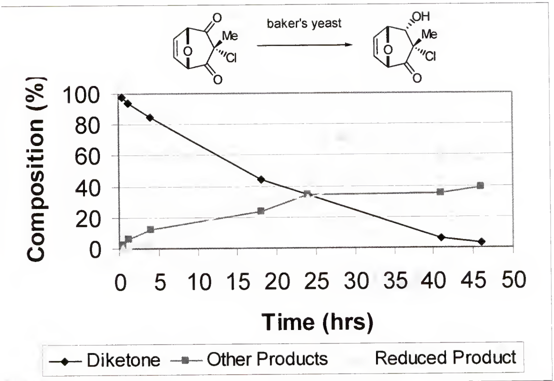
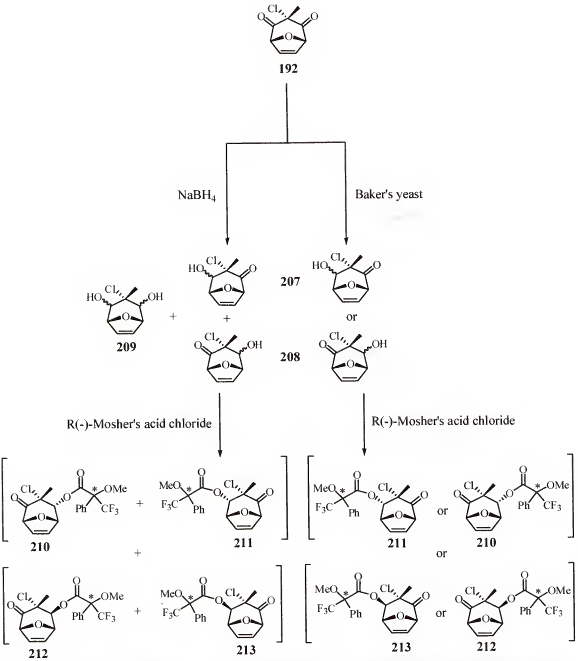


Figure 4-4. Reaction time course for the Baker's yeast reduction of **192** at pH 6.5

We started our investigation with material **192** because it was readily available. The goal for these experiments was to produce **207** as a single ketol product. This makes it essential that only one of the ketones be reduced, however for the purposes of this study it is not important which regioisomer is produced. Substrate **192** was added to the mature yeast cells and the reaction was monitored by GC/MS (Figure 4-4). At this point, we were not sure of the identity (by GC/MS) of all products produced from the fermentation other than the desired reduction product; therefore we labeled them as "other products" until further investigations were attempted. Under the initial conditions, it was possible to achieve complete consumption of the starting diketone in two days. It was also apparent that the formation of the "other products" was faster at the start of the reaction than reduction of the diketone. When the reaction was deemed complete, the cells were spun down in a centrifuge and the aqueous media was extracted overnight with ethyl acetate in a continuous extractor. Based on the GC/MS data, we were fairly confident that we had achieved mono-reduction but we needed to establish if there was any enantioselectivity associated with the reduction. This was accomplished by reacting **192** with sodium borohydride to chemically produce a 1:1 mixture of regioisomers **207** and **208** along with diol **209** (Scheme 4-7). The mixture was separated from the diol by flash chromatography on silica gel. The mixture of alcohols, as well as the product from the Baker's yeast reduction, were converted to the corresponding chiral esters using R(-)-α-Methoxy-α-trifluoromethyl-phenylacetic acid chloride (Mosher's acid chloride). In the reduction with sodium borohydride, a total four compounds could be generated. From results obtained from the alkylation experiments, we felt confident that delivery of the hydride had occurred from the *exo*-face of the molecule producing a mixture of **210** and **211** only. In the case of the yeast product, only two compounds should be obtained as a mixture of regioisomers as either **210**/**211** or **212**/**213** because the yeast should prefer one face of the molecule over the other. Upon examination of the ^{19}F NMR from the Mosher's ester compounds, it was found that the borohydride reduction had indeed



Scheme 4-7. Determination of enatioselectivity from the reduction with Baker's yeast

produced only two compounds in a ratio of almost 1:1, this demonstrated that attack of the hydride had occurred from only one face of the ketone to give **210** and **211** (Figure 4-5). When the Mosher's ester from the yeast reduction was examined only one peak was observed with almost no trace of anything else in the spectra, this correlated to an enantiomeric excess of >98%. In light of these findings we were confident in speculating

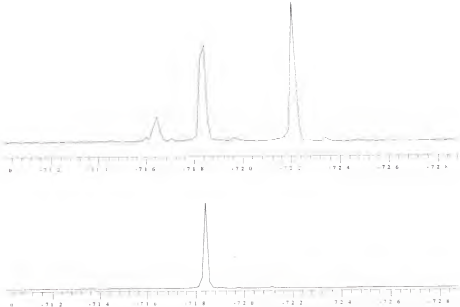
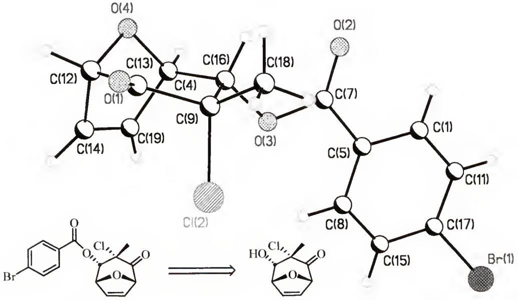


Figure 4-5. ^{19}F Mosher's ester data, Top-from $NaBH_4$; Bottom-Baker's yeast

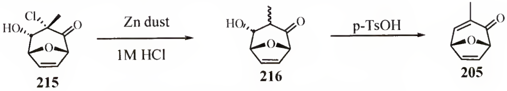
that the delivery of the hydride in the yeast reduction had occurred from the *exo*-face giving either **210** or **211**. Having established the relative stereochemistry, we needed to



214 **215**

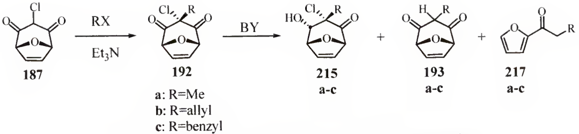
Figure 4-6. X-ray crystal structure of **214** and assignment of absolute stereochemisry

assign the absolute stereochemistry from the reduction. The alcohol from the fermentation was converted to a *p*-bromobenzoate ester in order to obtain a crystal for X-ray analysis. Fortunately, we were able to crystallize ester **214** and based on the X-ray structure the absolute stereochemistry was determined to be (S) (Figure 4-6). We were then in a position to synthesize enone **205** (Scheme 4-8). Various methods were examined to produce **205** from the chiral fermentation product **215** in a one pot procedure, but did not prove fruitful. A two step process was adopted, which involved the reduction of the chlorine, as before, with zinc dust and 1M HCl followed by isolation of intermediate **216** by continuous extraction. Removal of the chlorine produced a 1:1 mixture of *endo-*/*exo-*isomers α to the ketone. Elimination was triggered by adding a catalytic amount of p-tosic acid to a solution of **216** and letting stir for two days. Enone **205** was produced and detected by TLC and ^{1}H NMR but was discovered to be unstable and decomposed at room temperature after a short period of time.



Scheme 4-8. Synthesis of key intermediate **205**

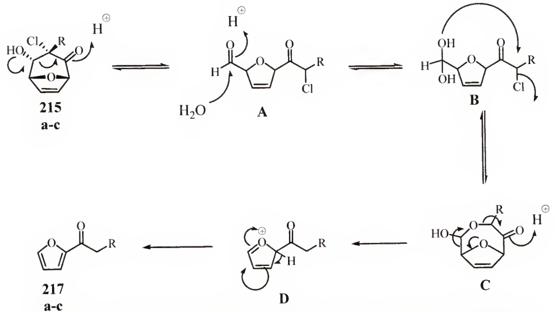
Having established the enatioselectivity of the reduction with Baker's yeast, we then set out to identify the so called "other products" from the fermentation and to explore our new methodology on other substrates. The belief was that in addition to reduction, dechlorination was occurring of the diketone, as well as degradation of the



Scheme 4-9. Examination of the scope of the BY reduction

reduced starting material (Scheme 4-9). This trend was observed in all cases examined (**192a-c**). The identification of the dechlorinated product **193a-c**, was determined by chemical reduction of **192a-c** with zinc and comparison of spectral data obtained. Both compounds, prepared independently, matched on all data examined. Interestingly, reduction of the dechlorinated material was never observed by GC/MS in spite of long reaction times. The mechanism by which the dechlorination occurred was unclear, but there is precedence for the microbial dehalogenation of organic compounds by dehalogenases.[59] Small molecules inside the cell that contain sulfur, such as cysteine and glutathione, may have been responsible for the dechlorination. This speculation was tested in two separate reactions involving **192a** and cysteine and glutathione. The dechlorinated products obtained from these reactions confirmed that something inside the cell, other than the reductase, was responsible for the dechlorination.

The appearance of the other furanyl byproduct **217** was first observed by GC/MS, in significant amounts, when substrates **192b** and **192c** were subjected to reduction by BY. Because of this, a second examination of the GC/MS data obtained from the reduction of **192a** showed the presence of this byproduct as well. The structure of this product was deduced from the mass spectrometry and NMR data obtained from isolation of a pure fraction of **217b**. To further confirm the structure, an authentic sample of **217b** was prepared by chemical methods. The comparison of NMR from both compounds matched and gave the same retention times by a co-injection on the GC/MS. It was postulated that the furanyl compounds **217a-c** arose from the degradation of the mono-reduced products **215a-c**. This was proposed because over the long reaction times the abundance of the reduction products decreased while the concentration of the furnayl compounds increased. The mechanism proposed for the formation of the furanyl byproduct is illustrated in Scheme 4-10. Based on the slightly acidic conditions required for the reduction (pH 6), an acid catalyzed retro aldol reaction could take place to open up the bicyclic system of **215** to give the dihydrofuranyl intermediate **A**. Tautomerization of the enol and hydration of the newly formed aldehyde by water affords **B**. Displacement of the chlorine α to the ketone by the hydrate produces **C**. Although the likelihood of this displacement is low, it does lead to an irreversible step that drives the reaction toward the production of the final product. Donation of a lone pair from the oxygen of the dihydrofuran ejects a molecule of formic acid and after tautomerization of

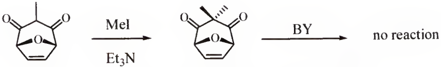


Scheme 4-10. Proposed mechanism for the formation of the furanyl byproduct

the resultant enol affords **D**. Finally, after aromatization to the furan, the degradation product **217a-c** is obtained.

In spite of the byproducts produced, successful reductions of **192b-c** were obtained. Determination of the enantioselectivity from the reductions was performed as before. Each ketol product was produced with an ee of >98% based on the examination of the corresponding Mosher esters by ^{19}F NMR and chiral GC.

Having examined different alkyl subsistents in the *exo*-position, we then wanted to replace the *endo*-chlorine with an alkyl appendage to establish if the reduction would still occur (Scheme 4-11). Removal of the chlorine was achieved as before with zinc/1M HCl, followed by installation of another methyl group from alkylation with methyl iodide gave **218**. Upon subjection to the reaction conditions with BY, no reduction was detected even with extended reaction times. This suggested that the molecule could not fit inside the active site of the enzyme responsible for the reduction due to the steric bias inflicted by the newly installed *endo*-methyl.



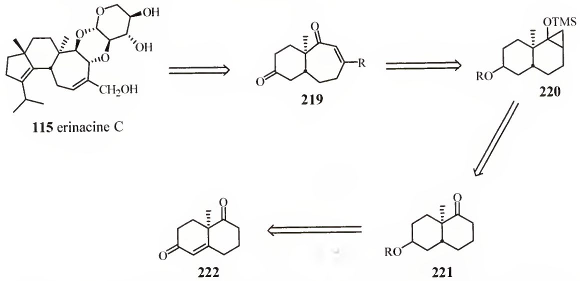
193 **218**

Scheme 4-11. BY reduction of **218**

Access to the Cyathane Core through the Wieland-Miescher Ketone

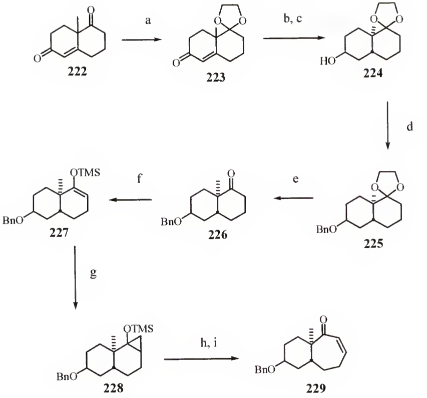
In addition to attempts to produce a total synthesis of one or more of the cyathanes, we were also interested in making derivatives of only the **B-C** ring system. We believe that the 6, 7-ring system is responsible for the biological activity demonstrated by the cyathanes. We hoped to produce analogs of the erinacines, sarcodonins, and scabronines for biological testing without the five-membered **A** ring.

Erinacine C was one of the target molecules chosen for this synthetic strategy (Scheme 4-12). Removal of the five-membered ring from the natural product results in **219**, which has the *trans*-6, 7 ring system. The seven-membered enone can be made in two steps by a ferric chloride catalyzed ring expansion of the TMS-cyclopropylether **220**, followed by elimination of the resultant β-chloro ketone.[10] Compound **220** can be obtained through cyclopropanation of the TMS-enol ether of **221**. The *trans*-fused 6, 6 ring system of **221** can be synthesized in a series of manipulations originating from the Wieland-Miescher ketone **222**. This ketone is a superb starting material because it can be obtained in a chiral form from a proline catalyzed Robinson annulation of 2-methyl-cyclohexane-1, 3-dione and methyl vinyl ketone.[60]



Scheme 4-12. Retrosynthesis of erinacine C **115** from the Wieland-Miescher ketone **222**

With this route in mind, we first wanted to perform a model study using racemic **222** because it was readily available. Selective ketalization of the Wieland-Miescher



(a) ethylene glycol, p-TsOH, molecular sieves, 91%; (b) Li wire, NH_3; (c) $NaBH_4$, MeOH, 83% two steps; (d) NaH, BnBr, THF, 90%; (e) p-TsOH, THF, H_2O, 96%; (f) LHMDS, TMSCl, Et_3N, THF, 97%; (g) Et_2Zn, CH_2I_2, CH_2Cl_2, 90%; (h) $FeCl_3$, pyridine, DMF; (i) NaOAc, MeOH

Scheme 4-13. Synthesis of racemic **B-C** ring system

ketone affords **223** as well as the bis-ketal and unreacted **222**. This mixture was easily separated by flash chromatography and the bis-ketal was hydrolyzed and recycled back through to produce additional **223**. A dissolving metal reduction of the double bond was used to set the *trans*-ring fusion in **224**, followed by reduction of the ketone. The newly formed alcohol was protected as a benzyl ether and the ketal was then removed by acid hydrolysis to afford **226**. Ketone **226** was converted to its' corresponding TMS-enol ether, which was used crude to install the cyclopropane of **228** by a carbene reaction. The seven-membered ring was produced by a one carbon ring expansion of **228** initiated by ferric chloride. The reaction gave the corresponding β-chloro cycloheptanone, which was then converted into enone **229.**

Conclusions

The purpose of this work was to establish the **B-C** ring system of the cyathane core in route toward a total synthesis or preparation of analogs for biological testing. Attempts to synthesize the *trans*-fused 6, 7 ring system from the Robinson annulation approach failed to provide the desired ring fusion. Producing instead the *cis*-fused 6, 7-ring system by X-ray analysis (**198**). The asymmetric reductions of 3-alkyl-3-chloro-disubstitiuted-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-diones by Baker's yeast were successful in generating the corresponding β-hydroxy ketones in high ee (>98%). Low yields were obtained from the reductions (<20%) but the results are comparable with previously published works of mono-cyclic 1, 3-diketones. Reduction of 3, 3-dimethyl-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione was not achieved based on steric arguments in the active site of the enzyme. Generation of enone **205** was accomplished but it was determined that the compound was not stable and decomposed after a short period of time at room temperature. Manipulations of the Wieland-Miesher ketone **222** was successful in producing the *trans*-fused 6, 7 ring system **229** of the cyathane core in racemic fashion.

CHAPTER 5
EXPERIMENTAL

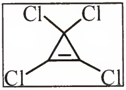
General Procedures

^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Gemini or a Mercury 300 at 300MHz and 75MHz respectively. All ^{19}F NMR were recorded on a VXR 300 at 300MHz. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in hertz using TMS (tetramethyl silane) as an internal standard. All spectra were obtained in $CDCl_3$ unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR as thin films between NaCl plates. The University of Florida Mass Spectroscopy Services performed all high-resolution mass spectra. Analytical GC-MS (EI) was performed using a Shimadzu GCMS-QP5000, that was equipped with a 5% phenyl column (30m, 0.25 mm ID, Restek Corp.) using the following conditions: 60 °C (2 min) to 250 °C (15 min) at 10 °C per minute. Chrial GC analysis was performed on a Hewlett-Packard 5890A capillary GC with a flame ionization detector and a Chrompack (25m, 0.25 mm ID) CP chirasil-Dex CB column. Elemental analysis was performed by Atlantic Microlabs (Norcross, Georgia). Melting points were measured on a Thomas-Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured from $CHCl_3$ solutions using a Perkin-Elmer 241 polarimeter operating at 20°C in a 1 dm cell. All commercial materials were used without purification unless otherwise noted. The following solvents were freshly distilled under positive pressure of dry nitrogen prior to use: tetrahydrofuran (THF), diethyl ether (Et_2O), benzene (PhH) and dimethoxyethane (DME) from potassiumbenzophenone ketyl; methylene chloride (CH_2Cl_2) and acetonitrile (CH_3CN) from calcium hydride (CaH_2). All reactions were performed in a flame dried flask under an inert atmosphere of argon (Ar) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica 60-F254 coated 0.25 mm plates. Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40-63 µm or 10-40 µm).

X-ray experimental: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in *SHELXTL6,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 146 parameters were refined in the final cycle of refinement using 2080 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 3.19% and 8.03%, respectively. Refinement was done using F^2.

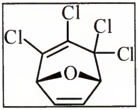
Two step procedure for tetrachlorocyclopropene[61] (185)



Pentachlorocyclopropane: A 3-L three-neck round bottom flask was charged with trichloroethylene (1.5M, 1.3L) and sodium trichloroacetate (350g, 1.89 mol). The flask was then fitted with a mechanical stirrer, reflux condenser and an internal thermometer. The solution was heated and left to equilibrate to 90-95°C overnight. The next day DME (9.5M, 200ml) was added and the mixture was left to stir for 1 week. During the reaction the temperature was maintained at 90-95°C and the solution gradually became dark brown. After 1 week, solution was allowed to cool and the solids were filtered off. The resultant blackish-brown solution was washed with copious amounts of water then dried ($MgSO_4$) and concentrated *in vacuo*. The crude brown liquid was then distilled under reduced pressure to give pentachlorocyclopropane (75g, 19%; bp_7 60°–64°C, lit. bp_7 56 °C). ^1H NMR (300MHz, $CDCl_3$) δ 3.91 (s, 1H). All other spectral data is in agreement with the literature values.

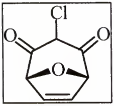
Tetrachlorocyclopropene **185**: A 250ml three-neck round bottom flask was fitted with a condenser, internal thermometer, and magnetic stir bar. KOH (86% assay, 27g, 419 mmol) was dissolved in water (18M, 23ml) and the glass was allowed to cool back to room temperature. Pentachlorocyclopropane (30g, 140 mmol) was then added and the solution was heated with a heat gun until initiation of an exothermic reaction was observed (temp. ca. 70 °C), the reaction was then maintained at a temperature of 88 °-92 °C with ice-water bath cooling and if needed heat gun. This heating/cooling was continued for 30min and then the reaction was cooled to 50 °C with a ice-water bath. Once cooled, the solution was poured into a 400ml beaker filled with ice (ca. 200ml), and concentrated HCl (50ml) was then added to bring the pH to 1-2. The mixture was then extracted with methylene chloride (3 X 20ml), washed with saturated sodium bicarbonate (ca. 50ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield tetrachlorocyclopropene as a light yellow lachrymatory liquid (17.4g, 70%) with no further purification needed. ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.4, 122.7. All other spectral data is in agreement with the literature values.

2,3,4,4-Tetrachloro-8-oxa-bicyclo[3.2.1]octa-2, 6-diene[12] (186)



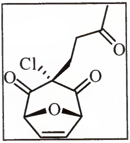
An oven dried 30ml glass sealed tube was charged with furan (8.1ml, 112.44 mmol), tetrachlorocyclopropene (10g, 56.22 mmol), and CCl_4 (4M, ca. 10ml) and sealed. The tube was heated in a sand bath at 80 °C for 15hr. The mixture was then poured into a 250 round bottom flask and the tube was rinsed with methylene chloride (ca. 20ml) and concentrated *in vacuo.* The viscous semi-sold was triturated with petroleum ether (ca. 100ml) and then the solvent was removed *in vacuo.* The semi-solid was again dissolved in petroleum ether (ca. 100ml) and the product was precipitated by cooling the solution to -78 °C by dry ice/acetone mixture for 30min. The liquid was removed by filtration and the solid was dried *in vacuo* to give **186** as a white solid (10.0g, 72%) with no further purification needed. Melting point, 59-60 °C, lit. 59-60 °C, all other spectral data is in agreement with the literature values.

3-Chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione[12] (187)



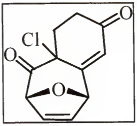
A 100ml beaker was charged with concentrated H_2SO_4 (10ml) and was heated to 90 °C in a silica oil bath equipped with a thermometer. Finely powdered **186** (3.0g, 12.10 mmol, crushed with a mortar and pestle) was added all at once to the preheated sulfuric acid. Liberation of HCl gas was observed immediately and the solution turned blackish-brown. The solution was stirred for 5-10 min and the reaction quenched by pouring the hot solution into a 250 ml beaker with an ice/water mixture and allowed to sit until all ice had melted. The aqueous solution was extracted with methylene chloride (3 X 15 ml), the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to provide **187** (0.936g, 45%) as a brown solid with no further purification needed. Melting point, 134-137 °C, lit. 139-140 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ 5.32 (s, 2H), 5.64 (s, 1H), 6.19 (s, 2H), all other spectral data is in agreement with the literature values.

3-Chloro-3-(3-oxo-butyl)-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (188)



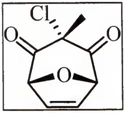
To a flame dried 10 ml round bottom flask containing THF (1M, 3 ml) and a magnetic stir bar was added **187** (0.5g, 2.89 mmol) and triethylamine (0.796 ml, 5.79 mmol). The solution was allowed to stir at room temperature for 30min then methyl vinyl ketone (freshly distilled 0.468 ml, 5.79 mmol) was added and stirred an additional 1.5hr. The reaction was monitored by TLC and judged to be complete after 1.5hr. The reaction was quenched with 1M HCl (2 ml) and extracted with ethyl acetate (3 X 10 ml). The organic extracts were combined, washed with saturated sodium bicarbonate (20 ml), washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford crude product as an oil. The crude oil was purified by flash chromatography on silica gel (15% ethyl acetate:hexanes) to yield **188** (510mg, 75%) as a white solid. The solid was recrystallized from ether/hexanes and submitted for X-ray analysis. Melting point, 143-144 °C; R_f=0.5 (Hexane/Ethyl acetate 65:35); ^{1}H NMR (300MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.58 (t, J=6.3, 2H), 2.70 (t, J=6.1, 2H), 5.34 (d, J=1, 2H), 6.41 (d, J=1, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 30.1, 33.8, 37.8, 81.6, 86.4, 132.9, 195.0, 206.6; IR: 3096, 1757, 1732, 1715,1369, 1172, 1082 cm^{-1}; Anal. Calcd. for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57. Found: C, 54.43; H, 4.58.

7-Chloro-12-oxa-tricyclo[7.2.1.0^{2,7}]dodeca-2, 10-diene-4, 8-dione (189ab)



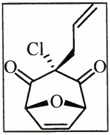
A flamed dried 10 ml round bottom flask was charged with THF (5 ml) and **188** (50 mg, 0.20 mmol). The solution was cooled to 0 °C and potassium *t*-butoxide (800 µl of a 1M sol. in THF, 0.80 mmol) was added as slowly at 0 °C. The cold bath was removed and the solution was left to stir overnight. The reaction was monitored by TLC and quenched with water. The solution was extracted with methylene chloride (3 X 5ml); the combined organic extracts were washed with saturated sodium bicarbonate (ca. 10ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude aldol product (32 mg, 70%) as oil. The oil was taken up in THF (10 ml) in a 25 ml round bottom flask. A catalytic amount of tosic acid (spatula tip) was then added and the solution was refluxed overnight. The reaction was monitored by TLC and was quenched with saturated sodium bicarbonate (ca. 10ml), dried ($MgSO_4$), and concentrated *in vacuo* to give crude **189ab** (20 mg, 70%) as a tan solid. R_f=0.24 (Hexane/Ethyl acetate 65:35); ^{1}H NMR (300MHz, $CDCl_3$) δ 0.81 (t, J=7.6, 1H), 1.63 (dd, J=3.1, 4.7, 1H); 2.03 (dd, J=3.1, 9.1, 1H), 3.00 (ddd, J=1.19, 4.87, 13.78, 1H), 4.09 (s, 1H), 5.27 (s, 1H), 5.46 (d, J=1.0, 1H), 5.60 (s, 1H), 6.50 (d, J=0.7, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 29.9, 33.8, 37.8, 45.1, 80.6, 117.9, 133.0, 133.3, 168.9, 188.4, 197.3; IR-3096,2959, 2920, 2849, 1718, 1704, 1260, 1094, 1035.

3-Chloro-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2,4-dione (192a)



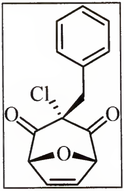
To a flame dried 10 ml round bottom flask was added **187** (600 mg, 3.47 mmol) and THF (3.5 ml). The solution was cooled to 0 °C and triethyl amine (0.98 ml, 6.95 mmol) was added drop wise and the solution was allowed to warm to room temperature for 10 min. Methyl iodide (0.65 ml, 10.42 mmol) was then added drop wise and the solution was stirred for 30 min. The reaction was monitored by TLC and quenched with 1M HCl. The aqueous layer was extracted with methylene chloride (3 X 5 ml), washed with saturated sodium bicarbonate (ca. 10 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a brown solid. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate:hexanes) to yield **192a** (454 mg, 70%) as a yellowish-clear solid. The compound was then recrystallized from diethyl ether and submitted for X-ray. Melting point 90-93°C; R_f=0.42 (35% ethyl acetate:hexane); ^1H NMR (300MHz, $CDCl_3$) δ 2.0 (s, 3H), 5.19 (s, 2H); 6.47 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 27.8, 76.1, 86.5, 132.7, 195.3; IR-3098, 1735, 1083, 931, 592 cm^{-1}; Anal. Calcd. for $C_8H_7ClO_3$: C, 51.50; H, 3.78; Found: C, 51.76; H, 3.86.

3-Allyl-3-chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (192b)



To a flame dried 25 ml round bottom flask was added **187** (2.00 g, 11.5 mmol) and THF (10 ml). The solution was cooled to 0 °C and triethyl amine (3.2 ml, 23.1 mmol) was added drop wise and the solution was allowed to warm to room temperature for 10 min. Allyl iodide (2.10 ml, 23.1 mmol) was then added drop wise and the solution was stirred overnight. The reaction was monitored by TLC and quenched with 1M HCl. The aqueous layer was extracted with methylene chloride (3 X 20 ml), washed with saturated sodium bicarbonate (ca. 30 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate:hexanes) to yield **192b** (1.7 g, 72%) as a clear oil. R_f=0.53 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 3.0 (d, *J*=7.2, 2H), 5.19 (m, 2H), 5.26 (s, 2H), 5.7 (m, 1H), 6.45 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 43.9, 78.4, 86.4, 121.3, 129.7, 132.9, 194.4; IR-N/A cm^{-1}; Anal. Calcd. for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27; Found: C, 56.50; H, 4.34.

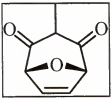
3-Benzyl-3-chloro-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (192c)



To a flame dried 25 ml round bottom flask was added **187** (1.5 g, 8.6 mmol) and THF (8 ml). The solution was cooled to 0 °C and triethyl amine (2.3 ml, 17.38 mmol) was added drop wise and the solution was allowed to warm to room temperature for 10 min. Benzyl bromide (2.0 ml, 17.38 mmol) was then added drop wise and the solution was stirred overnight. The reaction was monitored by TLC and quenched with 1M HCl. The aqueous layer was extracted with methylene chloride (3 X 20 ml), washed with saturated sodium bicarbonate (ca. 30 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a brownish solid. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate:hexanes) to yield **192c** (1.5 g, 68%) as a white solid. Melting point, 134-136°C, R_f=0.62 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 3.61 (s, 2H), 5.18 (s, 2H), 6.41 (s, 2H), 7.17 (m, 2H), 7.30 (m, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 45.5, 86.4, 128.24, 128.81, 130.6, 133.0, 133.1, 194.9; IR-

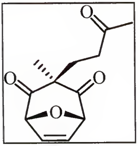
3106, 3068, 3032, 3008, 1732, 1456, 1079, 913, 741 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22; Found: C, 63.76; H, 4.25.

3-Methyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (193)



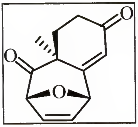
To a 5 ml round bottom flask was added **192** (100 mg, 0.53 mmol), Zn dust (70 mg, 1.07 mmol) and THF (1 ml). 1M HCl was added drop wise (ca. 10 drops) to the stirring slurry and reaction was observed immediately, indicated by the generation of heat. The reaction was monitored by TLC and deemed to be complete after 5 min. The solids were filtered through a pipette containing celite, diluted with water and continuously extracted with methylene chloride overnight. The methylene chloride was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **193** (60 mg, 73%) as a yellowish semi-solid. No further purification was done and the compound was used crude for all other reactions. R_f=0.25 (35% ethyl acetate:hexane); The reaction affords a mixture of *endo*/exo-isomers in a ration of 10:1 in the proton NMR: Major isomer: ^{1}H NMR (300MHz, $CDCl_3$) δ 1.25 (d, *J*=6.7, 3H), 4.05 (q, *J*=7.0, 13.73, 1H), 5.22 (s, 2H), 6.45 (s, 2H); minor isomer: ^{1}H NMR (300MHz, $CDCl_3$) δ 1.48 (d, *J*=7.9, 3H), 3.41 (q, *J*=7.9, 1H), 5.18 (s, 2H), 6.42 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 7.6, 59.1, 86.9, 132.4, 201.0; IR-3042, 1725, 1085 cm^{-1}

3-Methyl-3-(3-oxo-butyl)-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (194)



A 25 ml round bottom flask was charged with **193** (500 mg, 3.28 mmol) and THF (6.56 ml). The solution was cooled to 0 °C and triethylamine (0.54 ml, 3.94 mmol) was added drop wise and the solution was allowed to warm to room temperature for 5 min. Freshly distilled methyl vinyl ketone (0.32 ml, 3.94 mmol) was then added at room temperature and the reaction was stirred for 2 hr. The reaction was monitored by TLC and quenched with 1M HCl (ca. 5 ml). The aqueous layer was extracted with methylene chloride (3 X 5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give **194** (620 mg, 85%) as a yellowish-oil. R_f=0.61 (50% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.26 (s, 3H), 2.11 (s, 3H), 2.40 (t, *J*=7.2, 14.4, 2H), 2.48 (t, *J*=7.2, 14.6, 2H), 5.15 (s, 2H), 6.41 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 21.9, 30.2, 32.4, 62.2, 87.0, 132.9, 203.4, 207.2; IR-3094, 1725, 1715, 1172, 1082 cm^{-1}

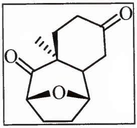
7-Methyl-12-oxa-tricyclo[7.2.1.0^{2,7}]dodeca-2, 10-diene-4, 8-dione (195ab)



A 15 ml two neck round bottom flask was fitted with a Dean-Stark trap filled with benzene and a condenser. To the flask was added **194** (100 mg, 0.45 mmol) and benzene (5 ml) under argon. The solution was cooled to 0 °C and freshly distilled pyrrolidine (0.037 ml, 0.449 mmol) was added. The solution became cloudy and the mixture was then heated to reflux for 15 min and the solution turned blood red. The reaction was monitored by TLC and quenched with 1M HCl. The aqueous layer was extracted with methylene chloride (3 X 5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give **195ab** (73 mg, 80%) as a tan solid. Melting point, 161-163°C; R_f=0.58 (50% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.52 (s, 3H), 2.09 (dd, *J*=6.9, 12.6, 1H), 2.20 (dd, *J*=2.3, 5.2, 1H), 2.55 (m, 2H), 4.85 (dd, *J*=0.7, 1.9, 1H), 5.25 (d, *J*=1.7, 1H), 5.78 (s, 1H), 6.50 (dd, *J*=1.7, 6.1, 1H), 6.54 (ddd, *J*=0.7, 1.9, 6.8, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 29.8, 30.5, 31.9, 33.9, 46.7, 85.3, 86.6, 122.9, 132.8, 134.9, 158.6, 198.2, 203.3; IR-3094, 2959, 2920, 2849, 1718, 1704, 1617, 1260, 1094, 1035 cm^{-1}

7-Methyl-12-oxa-tricyclo[7.2.1.$0^{2,7}$]dodecane-4, 8-dione (199)

This procedure is representative of the method that provided structure identification of **199** by X-ray analysis: A 5 ml round bottom flask was charged with **195ab** (50 mg, 0.25 mmol) and absolute ethanol (1 ml). The solution was degassed with argon and then 10% palladium on charcoal (2.5 mg, 0.025 mmol) was added. The flask was then fitted with a three way adapter equipped with a hydrogen filled balloon. The atmosphere inside the flask was evacuated with an aspirator and then filled with hydrogen from the balloon. This process was repeated twice more and the reaction was left to stir under a positive pressure atmosphere of hydrogen gas overnight. The reaction was complete as monitored by TLC the following day. The solution was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. This gave **199** (49 mg, 96%) as a yellowish-clear solid. The compound was recrystallized by slow evaporation of diethyl ether in the refrigerator and submitted for X-ray. R_f=0.55 (50% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.79 (m, 2H), 1.92 (m, 2H), 2.14 (m, 2H), 2.27 (m, 2H), 2.46 (dd, *J*=5.9, 15.2, 1H), 2.65 (dd, *J*=8.8, 14.7, 1H), 4.24 (d, *J*=7.6, 1H), 4.36 (d, *J*=1.4, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 28.7, 28.8, 29.3, 29.9, 32.7, 35.5, 43.5, 44.5, 45.9, 80.3, 81.3, 212.2, 214.6; IR-2923, 1710, 1465, 1044 cm^{-1}



General procedure for reductions using Baker's yeast[62]

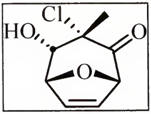
For all reactions a solution of 30 mM Bis-Tris (pH 6.0), 20 g/L sucrose, 9 g/L yeast and equimolar (to the substrate) γ-cyclodextrins was added to a flask that could hold at least twice the reaction volume. An autotitrator with 0.25 M NaOH was used to maintain the pH at 6.0. The reaction was incubated for one hour at room temperature.

For the reduction of **192a**, pre-treatment with ethyl 2-chloroacetoacetate was not necessary because there was no dechlorination observed during the reaction. The substrate (10mM) was added neat to the solution and the reaction was monitored as described below. This was the same method used for substrate **218**. Every 24 hours 20 g/L sucrose was added to maintain the yeast.

For the reduction of **192b** and **192c** the initial incubation was the same as **192a**. Then 1 mM ethyl 2-chloroacetoacetate was added neat to the solution. The treatment was incubated at room temperature for three hours. The cells were harvested by centrifugation (5000 X g) and the supernatant was discarded. A fresh solution of 30 mM Bis-Tris (pH 6.0), 20 g/L sucrose and γ-cyclodextrins was used to resuspend the cells and reconnected to the autotitrator. The substrate (5mM) was added neat to the solution and was monitored as described below. Every 24 hours 20 g/L sucrose was added to maintain the yeast. The yeast reduction reactions were monitored by taking a 300 μL aliquot from the solution and extracting with 100 μL of dichloromethane. A 1.0 μL portion of the organic phase was used for GC-MS analysis.

All reactions were continuously extracted for longer than 24 hours with ethyl acetate to isolate the products.

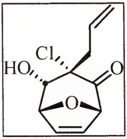
3-Chloro-4-hydroxy-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (215a)



Compound **192a** (500mg, 2.67 mmol) was reduced with Baker's yeast by the above procedure. The crude material isolated from the extraction was purified by flash chromatography on silica gel (25% ethyl acetate/hexane) to give **215a** (105 mg, 20%) as an off-white solid. Melting point 122-123°C; R_f=0.32 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ

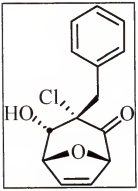
1.97 (s, 3H), 2.54 (d, J=4.6, 1H), 4.18 (bs, 1H, OH), 4.81 (dd, J=0.7, 2.0, 1H), 4.98 (ddd, J=0.5, 1.7, 5.8, 1H), 6.39 (ddd, J=0.7, 2.0, 7.1, 1H), 6.52 (ddd, J=0.9, 1.9, 7.1, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 27.7, 73.2, 73.9, 82.4, 84.9, 132.7, 134.0, 194.4; IR-3460, 3097, 2965, 1737, 1376, 1098, 1079, 1049, 920, 754.82, 552.40 cm^{-1}; Anal. Calcd. for $C_8H_9ClO_3$: C, 50.94; H, 4.81; Found: C, 51.50; H, 4.93; $[\alpha]^{20}_D$= -313.9 (c=0.0115, $CHCl_3$).

3-Allyl-4-hydroxy-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (215b)



Compound **192b** (500mg, 2.25 mmol) was reduced with Baker's yeast by the above procedure. The crude material isolated from the extraction was purified by flash chromatography (25% ethyl acetate/hexane) to give **215b** (100 mg, 20%) as a yellow oil. R_f=0.36 (35% ethyl acetate:hexane); ^1H NMR (300MHz, $CDCl_3$) δ 2.88 (m, 2H), 4.60 (d, J= 1.2, 1H), 5.16 (m, 1H), 5.20 (q, J=1.1, 1.7, 1H), 5.40 (dd, 0.7, 2.0,1H), 5.74 (m, 1H), 5.88 (ddd, J=0.4, 1.9, 5.9), 6.06 (ddd, J=0.7, 2.0, 7.0, 1H), 6.15 (ddd, J=0.7, 2.0, 7.0); ^{13}C NMR (75MHz, $CDCl_3$) δ 44.1, 70.1, 70.8, 82.2, 85.1, 121.1, 131.7, 132.7, 134.5, 194.2; IR 3436, 3088, 2958, 2923. 2854, 1732, 1639, 1260, 1098, 1019, 800-cm^{-1}; $[\alpha]^{20}_D$= -316 (c=0.012, $CHCl_3$).

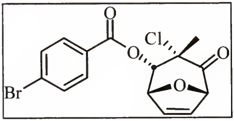
3-Benzyl-4-hydroxy-3-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (215b)



Compound **192c** (500mg, 1.90 mmol) was reduced with Baker's yeast by the above procedure. The crude material isolated from the extraction was purified by flash chromatography (25% ethyl acetate/hexane) to give **215c** (110 mg, 21%) as a white solid. Melting point, 115-117°C; R_f=0.36 (35% ethyl acetate:hexane);

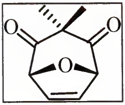
^{1}H NMR (300MHz, CDCl$_3$) δ 3.31, (d, *J*=13.7, 1H), 3.60 (d, *J*=14.0, 1H), 4.45 (d, *J*=4.9, 1H), 4.7 (t, *J*=0.9, 1.5, 1H), 4.87 (dd, *J*=1.6, 4.9, 1H), 6.42 (dd, *J*=2.1, 6.0, 1H), 6.52 (dt, *J*=0.9, 1.4, 6.0) 7.29 (m, 5H) ;^{13}C NMR (75MHz, CDCl$_3$) δ 44,4, 69.2, 75.8, 82.0, 85.1, 127.8, 128.9, 131.0, 133.0, 134.5, 134.9, 194.5; IR 3460, 3028, 2961, 2925, 1731, 1454, 1260, 1076, 1056, 762-cm^{-1}; $[\alpha]^{20}_D$= -296 (c=0.012, CHCl$_3$).

4-Bromo-benzoic acid 3-chloro-3-methyl-4-oxo-8-oxa-bicyclo[3.2.1]oct-6-en-yl ester (214)



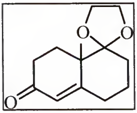
To a flame dried 5 ml round bottom flask was added **215a** (150mg, 0.795 mmol) and methylene chloride (1 ml) under argon. Triethylamine (0.167 ml, 1.19 mmol) and a catalytic amount of DMAP (ca. 10 mg) followed by addition of 4-bromo-benzoyl chloride (261 mg, 1.193 mmol). An immediate reaction was observed as indicated by formation of a white precipitate. The reaction was monitored by TLC, quenched with 1M HCl (ca. 1ml) and diluted with water (5 ml total volume). The aqueous layer was extracted with methylene chloride (3 X 5 ml), dried (MgSO$_4$) and concentrated *in vacuo*. The resultant oil was purified by flash chromatography on silica gel (20% ethyl acetate/Hexanes) to give **214** (251 mg, 85%) as a white solid. The product was then recrystallized from slow evaporation of diethyl ether in the refrigerator and submitted for X-ray analysis. Melting point 94-95°C; R$_f$=0.62 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, CDCl$_3$) δ 1.83 (s, 3H), 4.92 (d, *J*=1.7, 1H), 5.19 (dd, *J*=1.5, 5.1, 1H), 5.95 (d, *J*=5.4, 1H), 6.50 (dd, *J*=1.7, 5.6, 1H), 6.54 (dt, *J*=0.7, 6.1, 1H), 7.62 (d, *J*=8.3, 2H), 7.95 (d, *J*=8.5, 2H); ^{13}C NMR (75MHz, CDCl$_3$) δ 29.1, 69.5, 73.3, 80.0, 85.1, 128.0, 129.2, 131.6, 132.2, 132.7, 134.1, 164.8, 183.2, 194.1; IR-3104, 2966, 1737, 1726, 1586, 1264, 1106, 1082, 753cm^{-1}; Anal. Calcd. for $C_{15}H_{12}ClBrO_3$: C, 48.37; H, 3.25; Found: C, 48.37; H, 3.27; $[\alpha]^{20}_{D}$= -142 (c=0.004, $CHCl_3$).

3,3-Dimethyl-8-oxa-bicyclo[3.2.1]oct-6-ene-2, 4-dione (218)



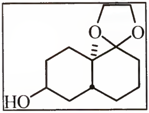
A 25 ml round bottom flask was flamed and charged with **193** (389 mg, 2.55 mmol) and THF (5ml). The solution was cooled to 0°C and DBU (0.57 ml, 3.8 mmol) was added drop wise. The solution was allowed to warm to room temperature and then methyl iodine (0.24 ml, 3.8 mmol) was added. The reaction was monitored by TLC and quenched with 1M HCl (ca. 5ml); the aqueous layer was then extracted with methylene chloride (3 X 5 ml). The combined organics were washed with saturated sodium bicarbonate (ca. 10 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give **218** (367 mg, 87%) as a yellow solid. Melting point 63-65°C; R_f=0.45 (35% ethyl acetate:hexane); ^1H NMR (300MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.45 (s, 3H), 5.14 (d, *J*=0.9, 2H), 6.37 (d, *J*=0.9, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 22.1, 26.1, 59.4, 87.0, 132.5, 203.7; IR-3094, 2985, 2935, 2872, 1737, 1713, 1581, 1263, 1105, 1070 cm^{-1}; HRMS (EI) Calcd. for $C_9H_{10}O_3$: 166.0630; Found: 166.0622.

Wieland-Miesher mono-ketal (223)[63]



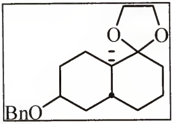
A 100 ml round bottom flask was charged with molecular sieves and flame dried under vacuum, let cool and relieved with argon. The Wieland-Miesher ketone **222** (1.4 g, 8.0 mmol), anhydrous ethylene glycol (40 ml) and p-TsOH acid (1.53 g, 8.0 mmol) were then added and let stir for 15 min. The reaction was then stopped by quickly filtering the solution through a coarse frit and pouring the filtrate into cold saturated sodium bicarbonate (ca. 150 ml). The aqueous layer was extracted with ethyl acetate (6 X 25 ml), the combined organics dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a mixture of mono- and bis-protected ketones. The viscous oil was purified by flash chromatography on silica gel (15% ethyl acetate:hexane) to give **223** (1.64 g, 91%) as a clear liquid. R_f=0.23 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.60-2.62 (m, 10H), 3.99 (d, 4H), 5.81 (s, 1H); all other spectral data are in agreement with literature values.

6-Hydroxy-1, 1-(1, 2-ethylenedioxy)-8a-methyl-octahydro-naphthalene (224)[64]



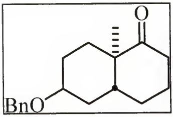
A 250 three neck flask was fitted with a dewar type condenser, the joints were then wrapped with Teflon tape and the whole apparatus was flamed under argon. After cooling to room temperature, a mixture of dry ice/acetone was placed in dewar to bring the temperature of the condenser to -78°C. Liquid ammonia (ca. 75 ml) was then condensed into the flask and freshly cut lithium wire (300 mg, 44.4 mmol) was then added and the solution became a dark blue color. A separate flame dried 50 ml pear shaped flask was charged with **223** (1.6 g, 7.4 mmol), *t*-butanol (1.4 ml, 14.8 mmol) and THF (15 ml). This solution was added drop wise to the Li/NH_3 solution by syringe over a period of 30 min. The reaction was left to stir for an additional 30 min, keeping the dewar condenser filled with dry ice/acetone. The reaction was quenched by cooling the stirring blue solution to -78°C and adding solid ammonium chloride (ca. 10 g) to the solution over a period of 45 min. When no blue color was visible in the reaction flask, saturated sodium bicarbonate (30 ml) was added and the two dewars were removed and the solution was let warm to room temperature. The flask was left open in the hood overnight so as to evaporate the excess solvent. The resultant white solids were diluted with water and extracted with diethyl ether (3 X 20 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the corresponding saturated ketone (1.49 g, 98%) as a clear oil. This crude product was immediately dissolved into methanol (65 ml) in a 250 round bottom flask, which was cooled to 0°C. Sodium borohydride (270 mg, 7.15 mmol) was then added and stirred for 30 min. The reaction was monitored by TLC and when the reaction was complete, the methanol was removed *in vacuo*. The residue was diluted with water, extracted with ethyl acetate (3 X 20 ml), the organics were combined and dried ($MgSO_4$) and concentrated *in vacuo* to give **224** (1.30 g, 85%, 83% for two steps) as a clear thick oil. R_f=0.45 (50% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.0 (s, 3H), 1.2-1.98 (m, 10H), 3.6 (m, 1H), 3.99 (m, 4H); all other spectral data are in agreement with literature values.

6-Benzyloxy-1, 1-(1, 2-ethylenedioxy)-8a-methyl-octahydro-naphthalene (225)



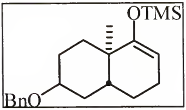
A 250 three neck round bottom flask was fitted with an addition funnel and flame dried under argon. Sodium hydride (2.16 g, 54.13 mmol, 60% dispersion in mineral oil) was added and washed with pentane (3 X 10 ml) to remove the mineral oil coat. The flask was then cooled to -78°C and THF (30 ml) was added. In a separate flame dried 100 ml pear shaped flask was added **224** (10.2 g, 45.11 mmol) and THF (60 ml). The solution was then transferred by cannula to the addition funnel and added drop wise overnight. The next day, benzyl bromide (5.9 ml, 49.62 mmol) was added to the addition funnel and added drop wise. After complete addition, the reaction was monitored by TLC and upon completion, quenched with cold water (ca. 30 ml). The aqueous layer was extracted with methylene chloride (3 X 25 ml), the combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a yellowish oil. The compound was purified by flash chromatography on silica gel (25% ethyl acetate/hexanes) to afford **225** (12.8g, 90%) as a clear thick oil. R_f=0.51 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.0 (s, 3H), 1.20-1.99 (m, 13H), 3.38 (m, 1H), 3.92 (m, 4H), 4.58 (s, 2H), 7.3 (m, 5H); ^{13}C NMR (75MHz, $CDCl_3$) δ 14.4, 23.3, 28.0, 28.1, 28.7, 30.8, 34.5, 39.8, 42.3, 65.1, 65.3, 70.0, 77.7, 113.0, 127.5, 127.7, 128.4, 139.2; IR-2932, 2866, 1456, 1110, 1052cm^{-1}; HRMS (EI) Calcd. for $C_{20}H_{28}O_3$: 316.2038; Found: 316.2036.

6-Benzyloxy-8a-methyl-octahydro-naphthalen-1-one (226)



A 500 ml round bottom flask was fitted with a condenser and charged with **225** (9.2g, 29.1 mmol), p-TsOH (1.65g, 8.7 mmol), and a 1:1 mixture of water/THF (145 ml). The solution was refluxed and the reaction monitored by TLC until complete (ca. 2-4 hrs). The heat was removed and the flask cooled to 0°C. The solution was then poured into a beaker containing ice and saturated sodium bicarbonate (ca. 30ml). The aqueous layer was extracted with ethyl acetate (3 X 20 ml). The combined organics were dried ($MgSO_4$), and concentrated *in vacuo* to give **226** (7.63 g, 96%) as a clear thick oil. R_f=0.46 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.41-1.50 (m, 5H), 1.59-1.72 (m, 3H), 1.83-1.90 (m, 2H), 1.99-2.05 (m, 2H), 2.22 (m, 1H), 2.63 (m, 1H), 3.30 (m, 1H), 4.58 (s, 2H), 7.24-7.30 (m, 1H), 7.31-7.33 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 15.8, 26.32, 27.6, 30.9, 33.8, 37.5, 43.9, 48.0, 70.1, 77.23, 127.5, 127.6, 128.4, 138.9, 215.8; IR-3029, 2934, 2862, 1704, 1698, 1453, 1111, 1071 cm^{-1}; HRMS (EI) Calcd. for $C_{18}H_{24}O_2$: 272.1776; Found: 272.1783.

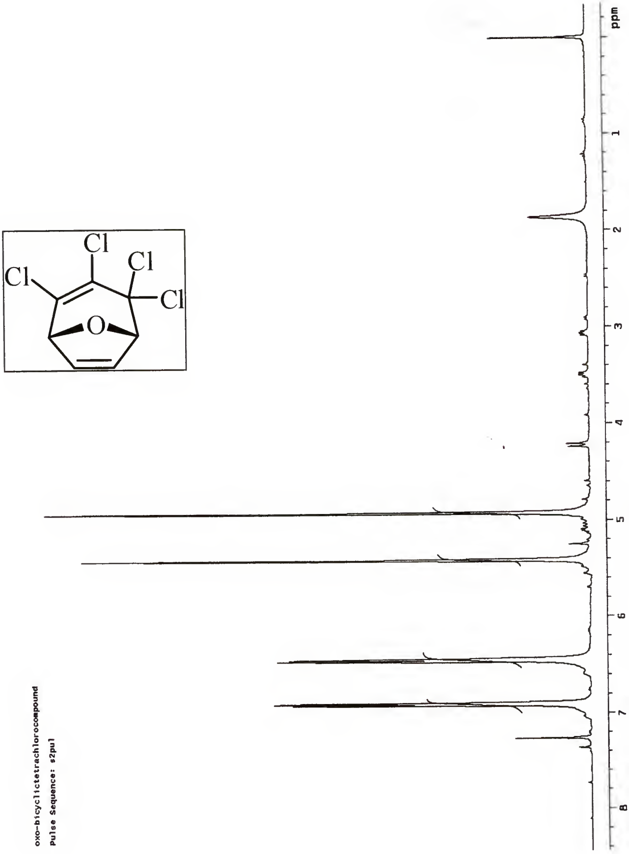
(6-Benzyloxy-8a-methyl-3, 4, 4a, 5, 6, 7, 8, 8a-octahydro-naphthalen-1-yloxy)-trimethyl-silane (227)



A 50 ml round bottom flask was flamed under argon and charged with freshly distilled 1, 1, 1, 3, 3, 3-Hexamethyl-disilazane (1.07 ml, 5.13 mmol) and THF (5 ml). The solution was cooled to 0°C and n-butyl lithium (2.07 ml of a 2.38M solution, 4.77 mmol) was added and the solution warmed to room temperature for 10 min. A separate 10 ml pear shaped flask was flamed under argon and charged with **226** (1.0 g, 3.67 mmol) and THF (5 ml). This solution was added drop wise to the flask containing LHMDS and stirred at room temperature for 15 min. A 1:1 solution of TMSCl/Et_3N (1 ml) was then added and the solution turned white after a few minutes. The reaction was monitored by TLC and quenched with saturated ammonium chloride (ca. 10 ml). The product was extracted with diethyl ether (3 X 10 ml). The organics were combined, dried (Na_2SO_4), and concentrated *in vacuo* to give **227** (1.22 g, 97%) as a pale yellow oil. R_f=0.85 (35% ethyl acetate:hexane); ^{1}H NMR (300MHz, benzene-d_6) δ 0.12 (s, 9H), 1.01 (s, 3H), 1.05-2.01 (m, 11H), 3.20 (m, 1H), 4.38 (s, 2H), 4.54 (dd, J=2.8, 4.7, 1H), 7.02 (m, 4H), 7.13 (d,1H); ^{13}C NMR (75MHz, benzene-d_6) δ 0.4, 2.6, 17.4, 24.31, 25.6, 28.4, 33.5, 34.4, 38.3, 41.59, 69.9, 78.1, 100.0, 127.3, 127,5, 128.4, 140.1, 158.5; IR-3031, 2936, 2861, 1655, 1453, 1250, 1201 cm^{-1}; HRMS (EI) Calcd. for $C_{21}H_{32}O_2Si$: 344.2171; Found: 344.2170.

APPENDIX A
SELECTED SPECTRA

The NMR (^{1}H and ^{13}C) spectra of 18 selected compounds are graphically portrayed in this section. The spectra are displayed along with the intended structure.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7
8
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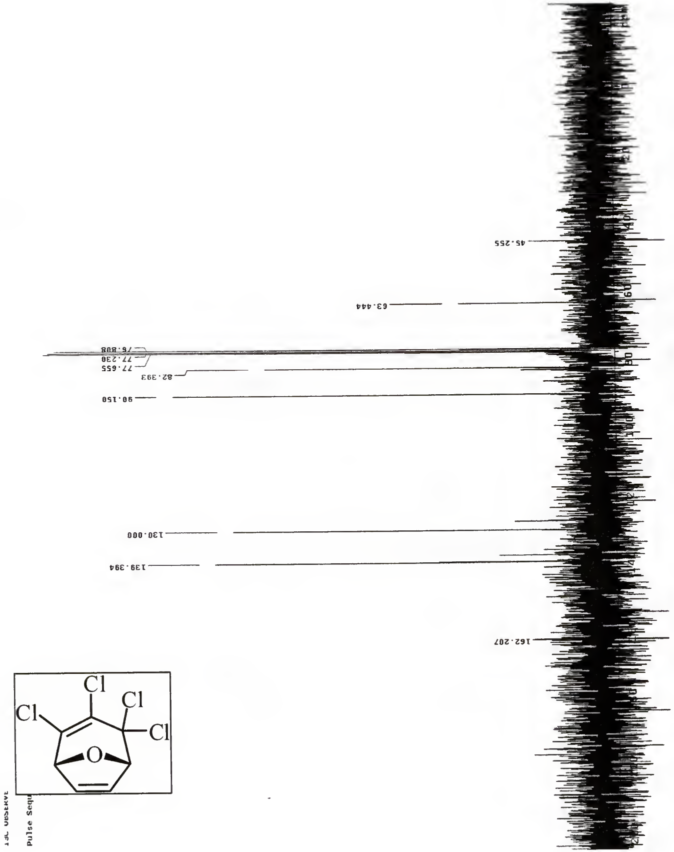
1.00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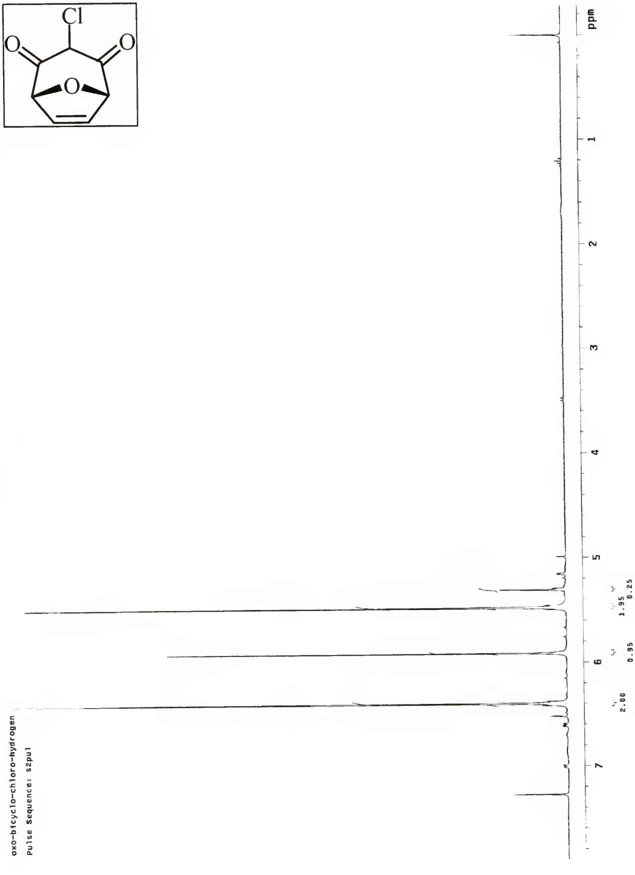
13C OBSERVE
Pulse Sequ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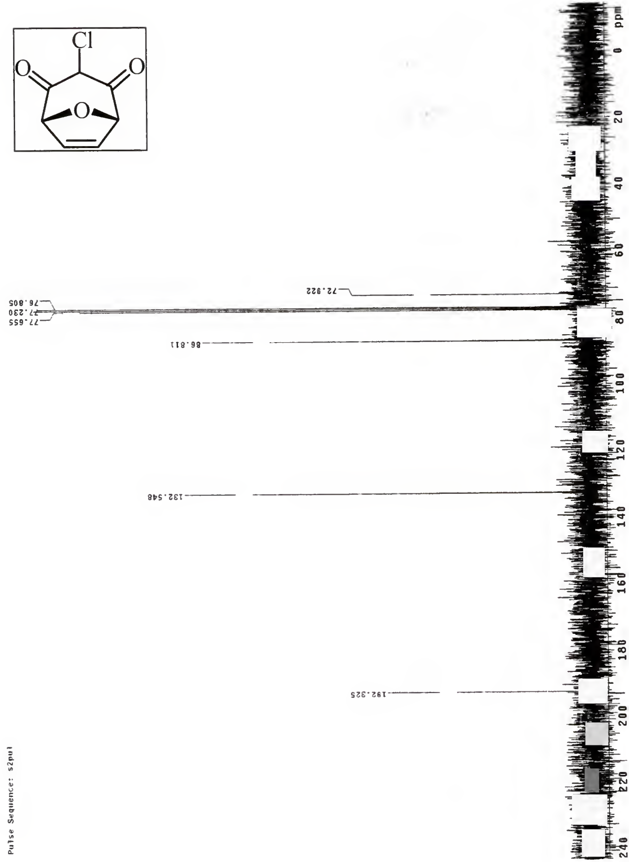
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220
240
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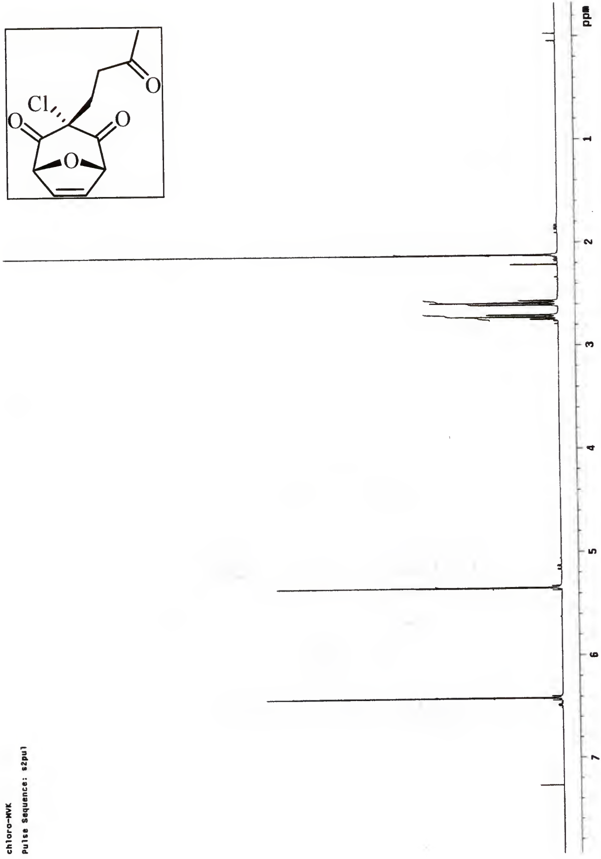
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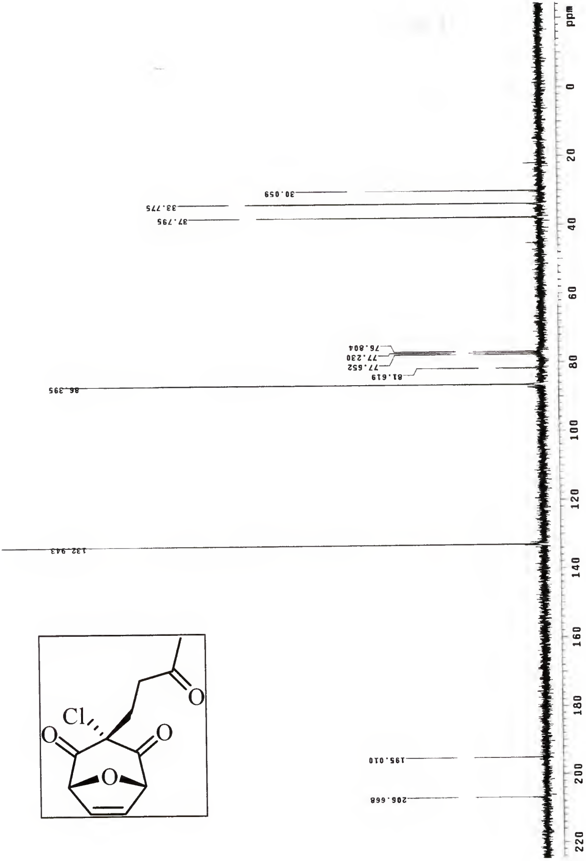
2.00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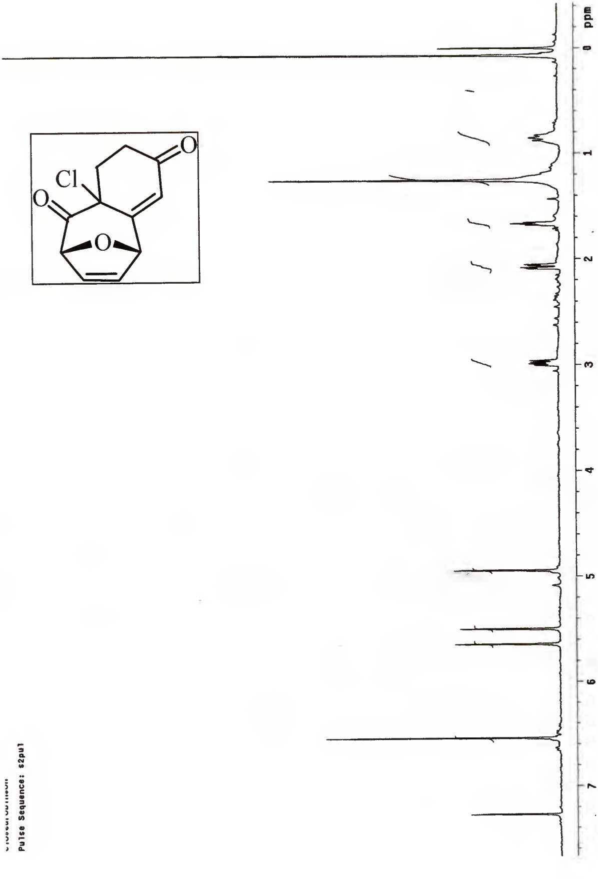
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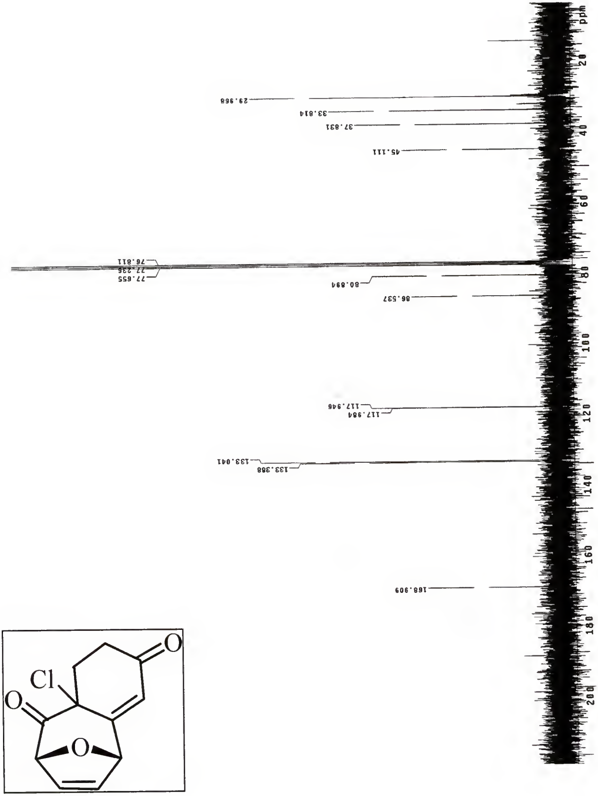
2.00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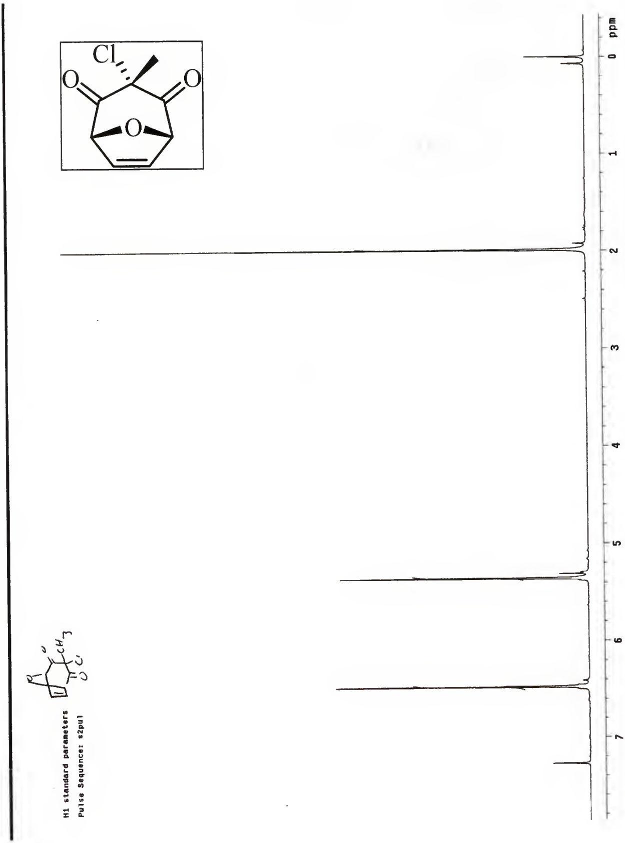
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H1 standard parameters
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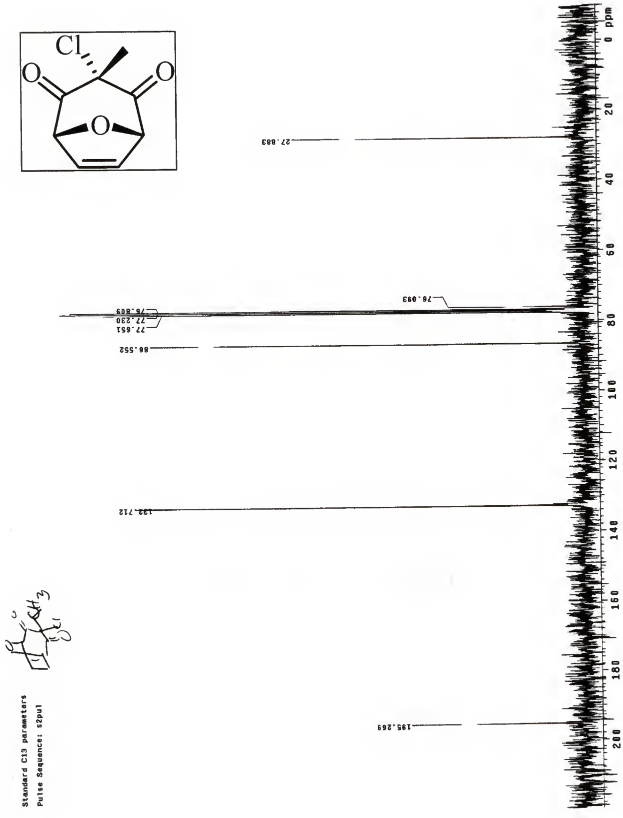
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Standard C13 parameters
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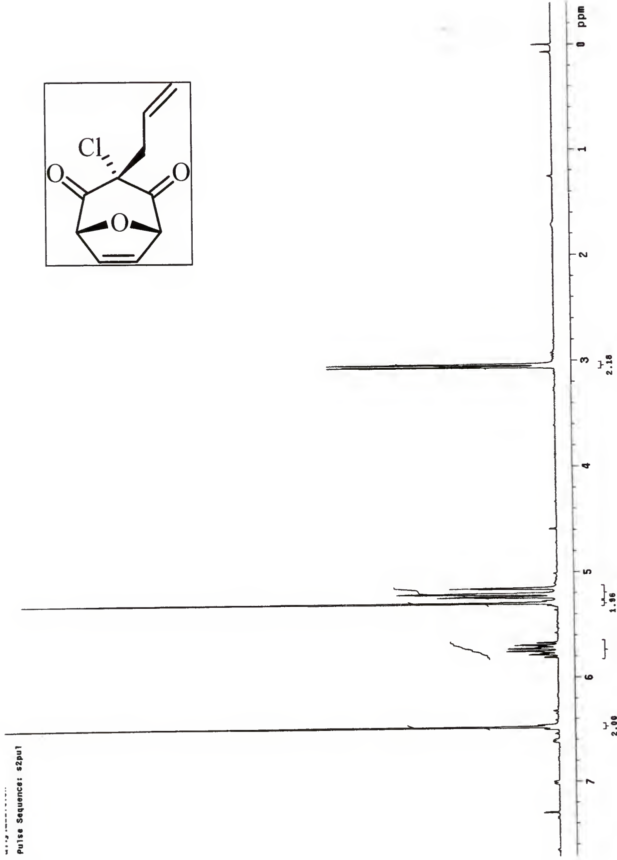
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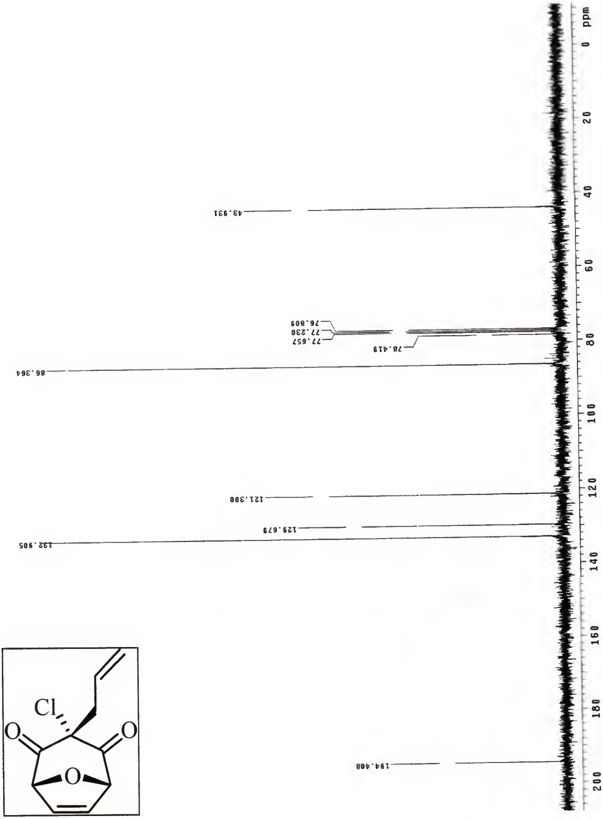
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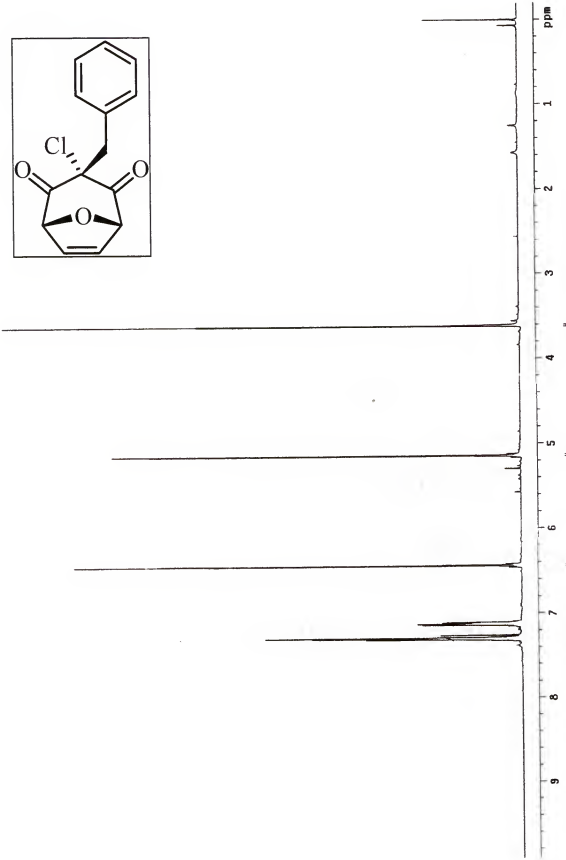
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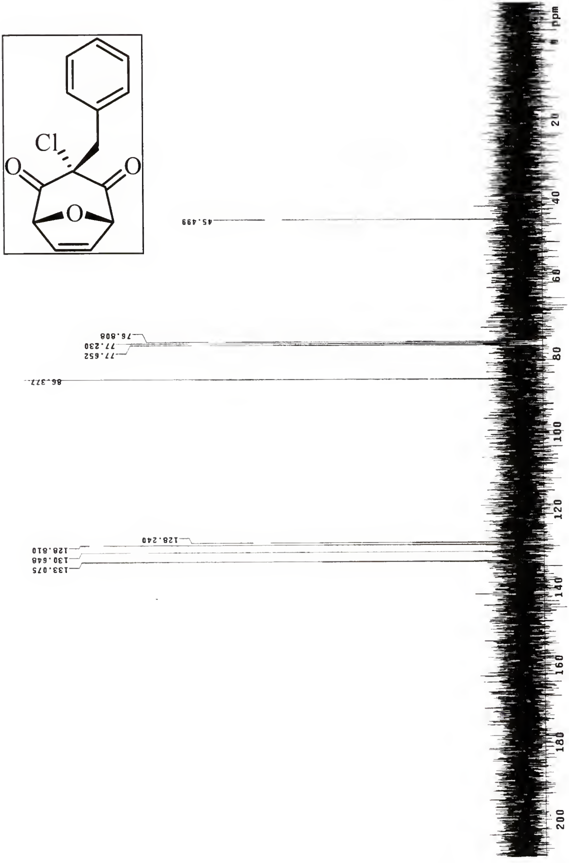
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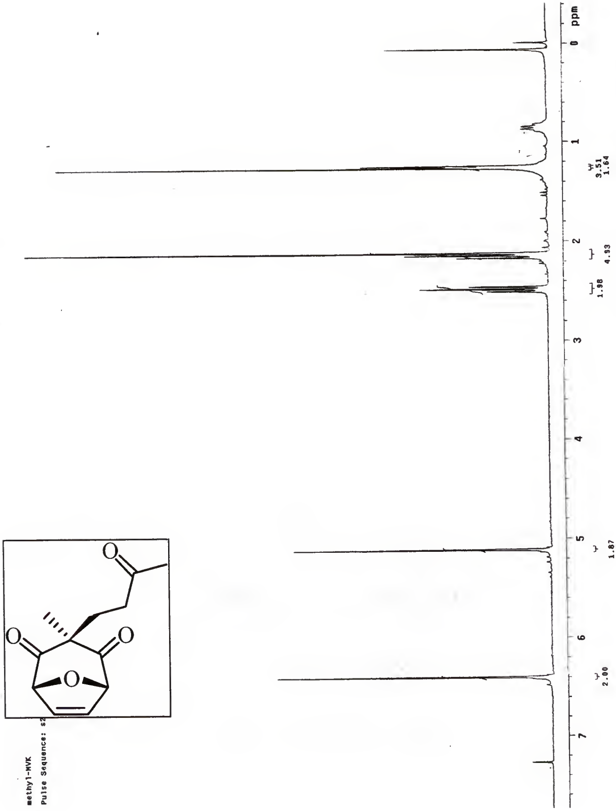
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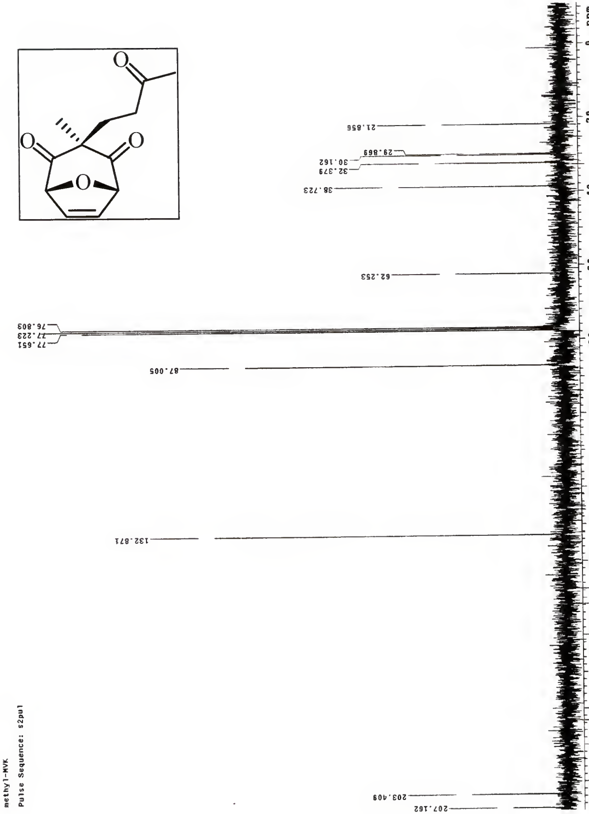
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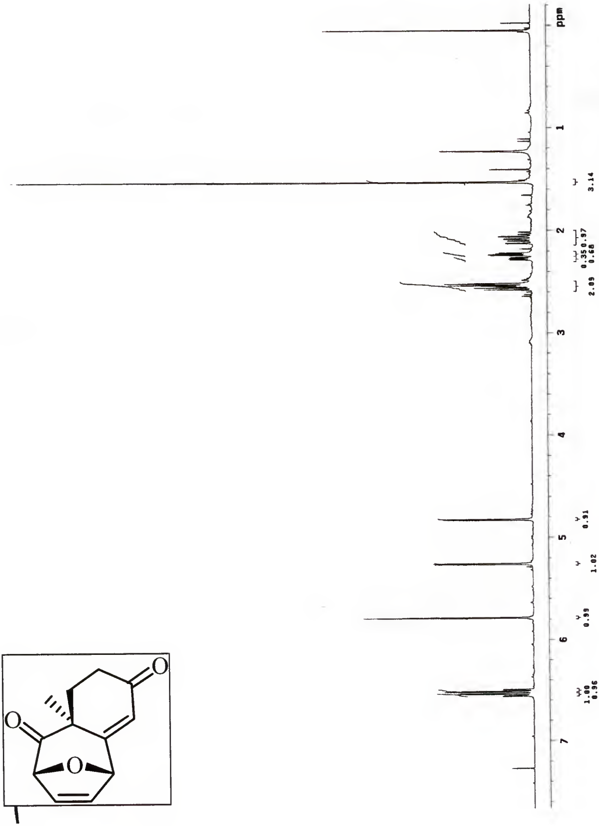
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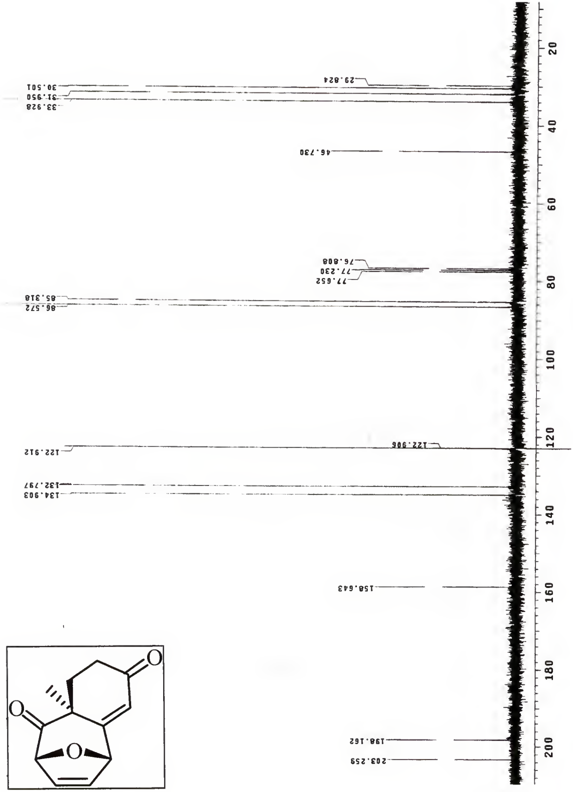
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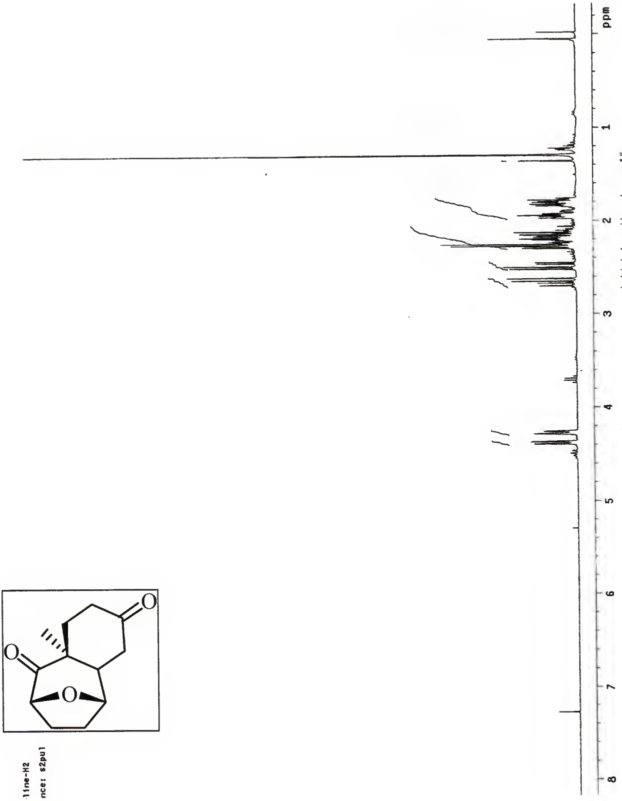
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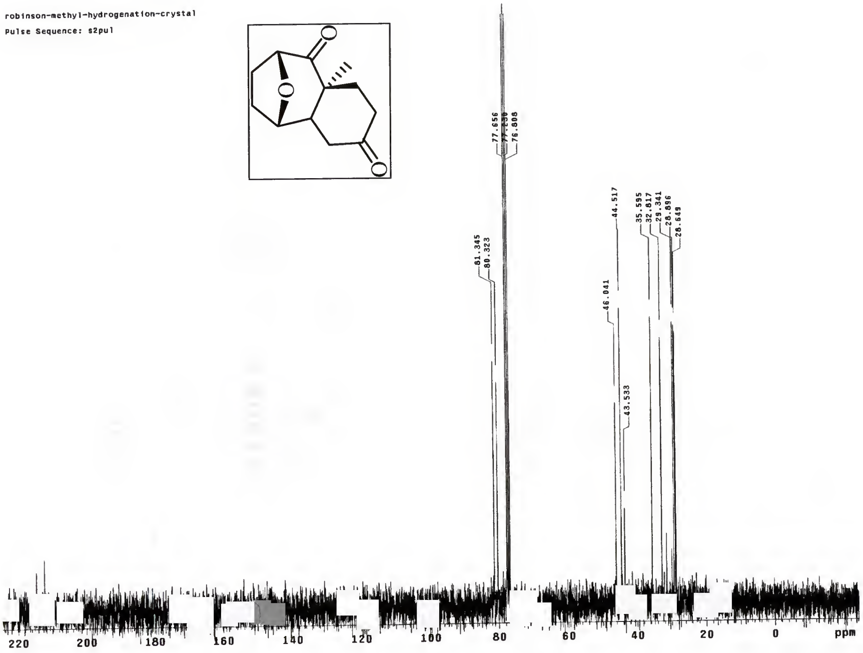
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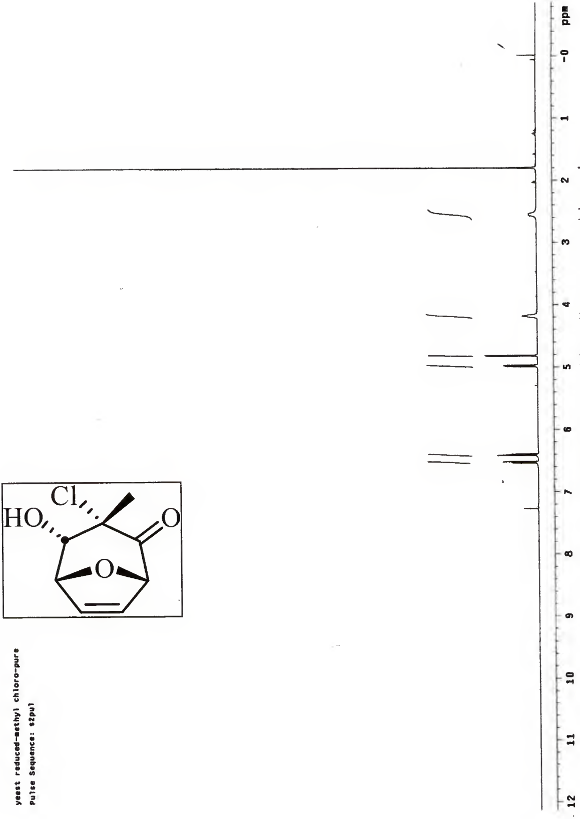
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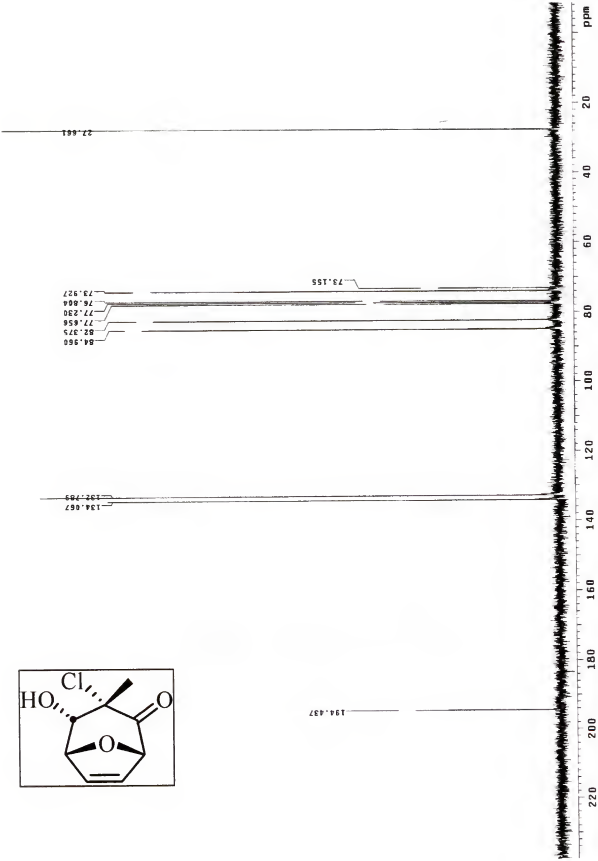
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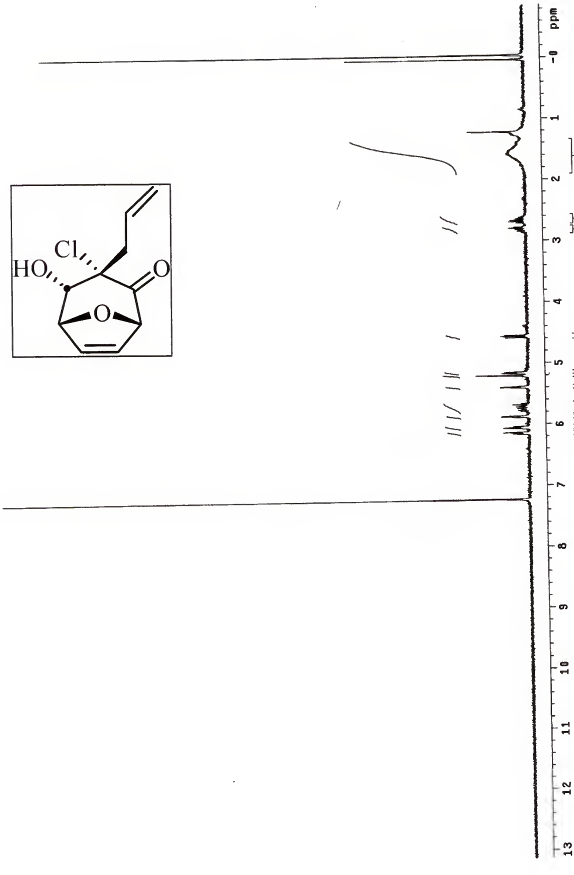
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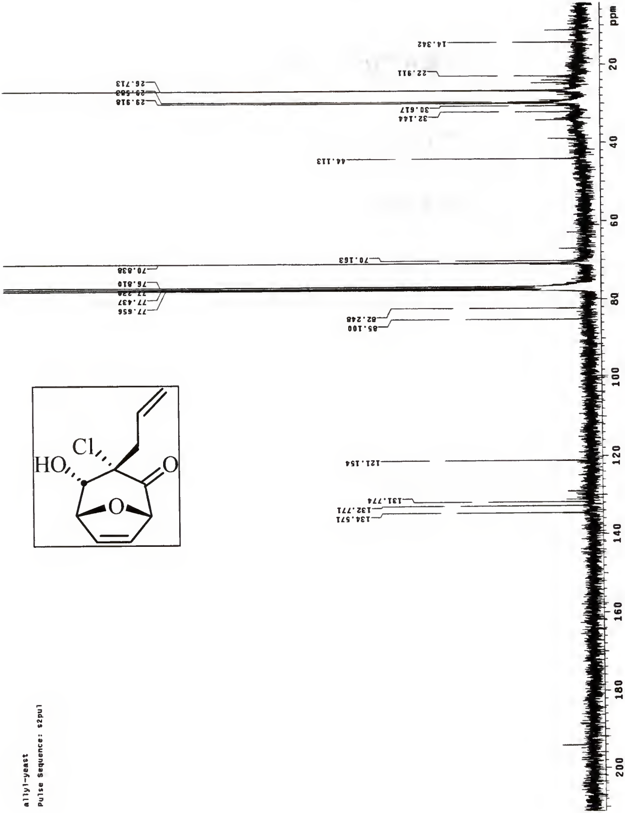
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77.656
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85.100
121.154
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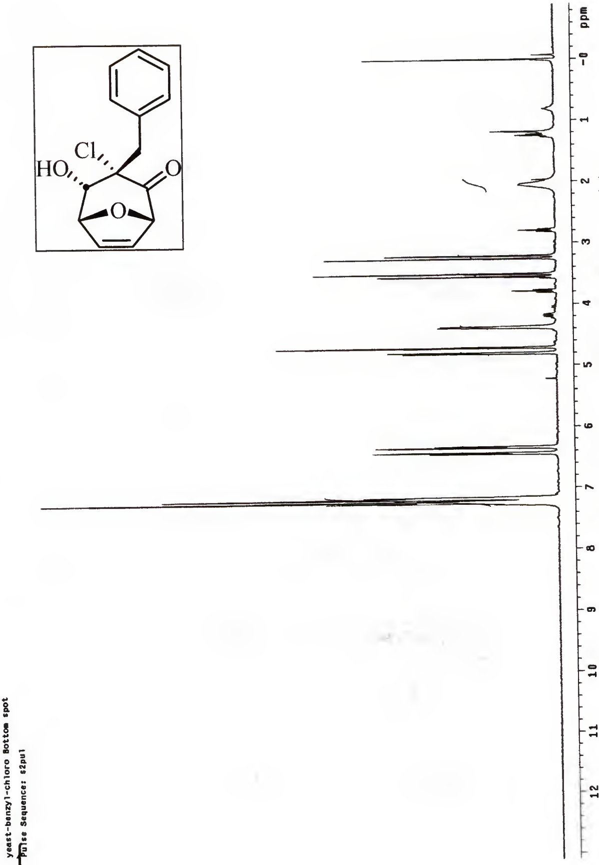
Cl
HO
O
O
yeast-benzyl-chloro Bottom spot
Pulse Sequence: s2pul
ppm
-0
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2
3
4
5
6
7
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1.03
0.96
1.00
1.01
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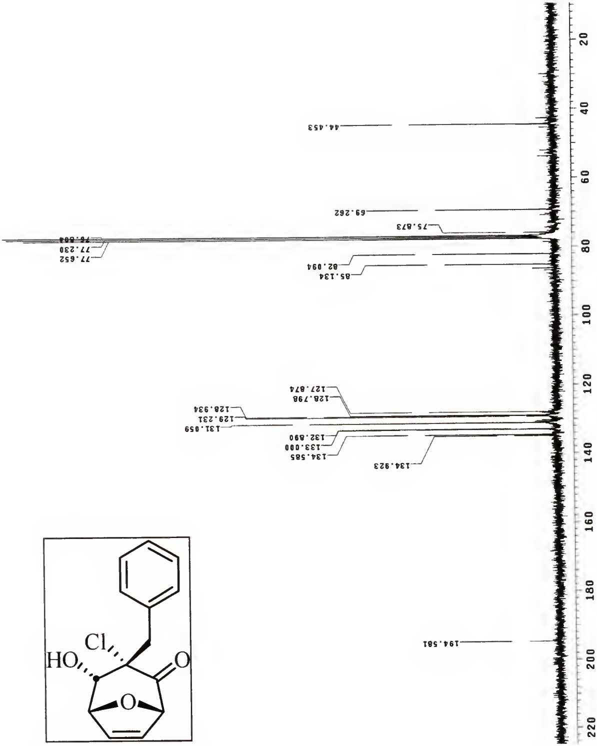
1.00
5.91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132.890
133.000
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140
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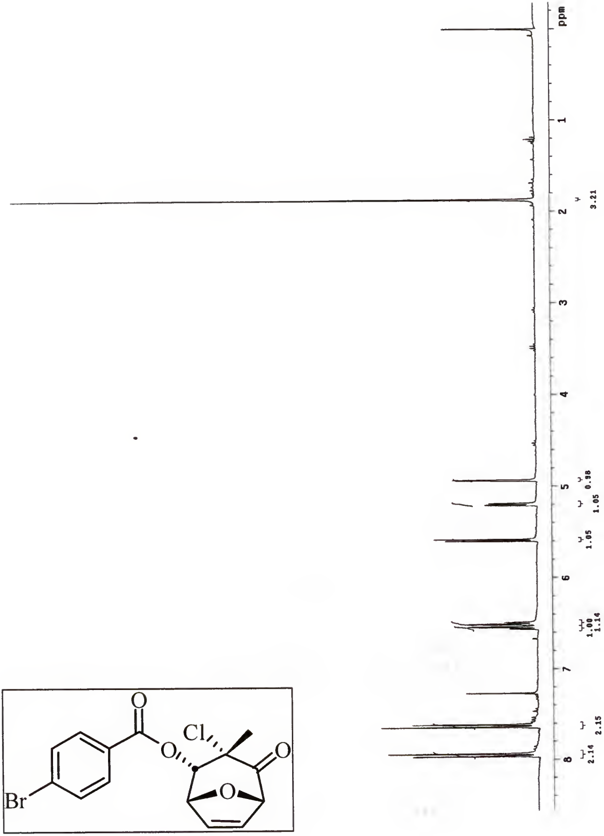
220
Cl
HO
O
O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2.14
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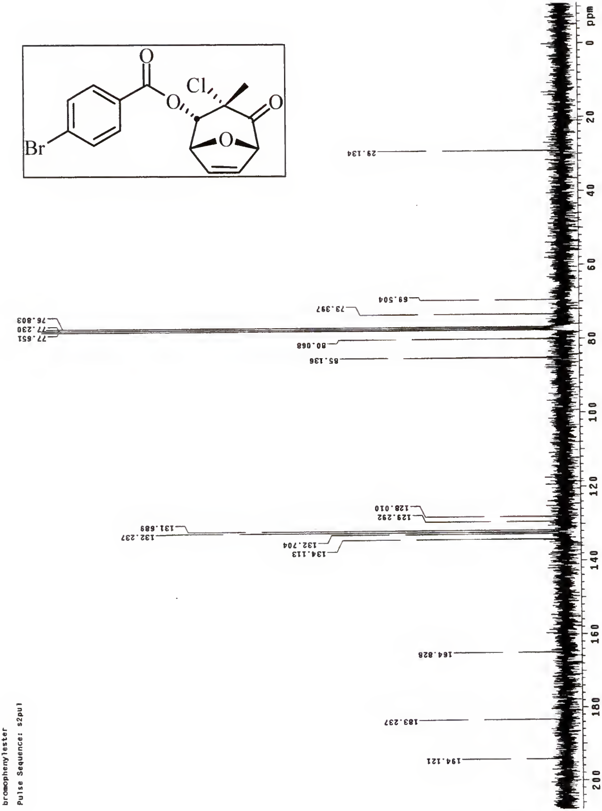
Cl
O
O
O
Br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Cl
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128.010
129.292
131.689
132.237
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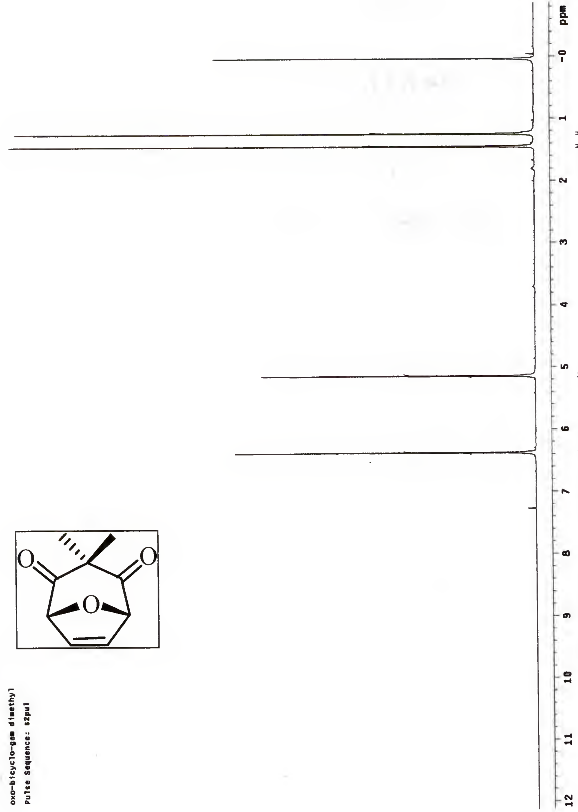
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Pulse Sequence: s2pul
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2
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4
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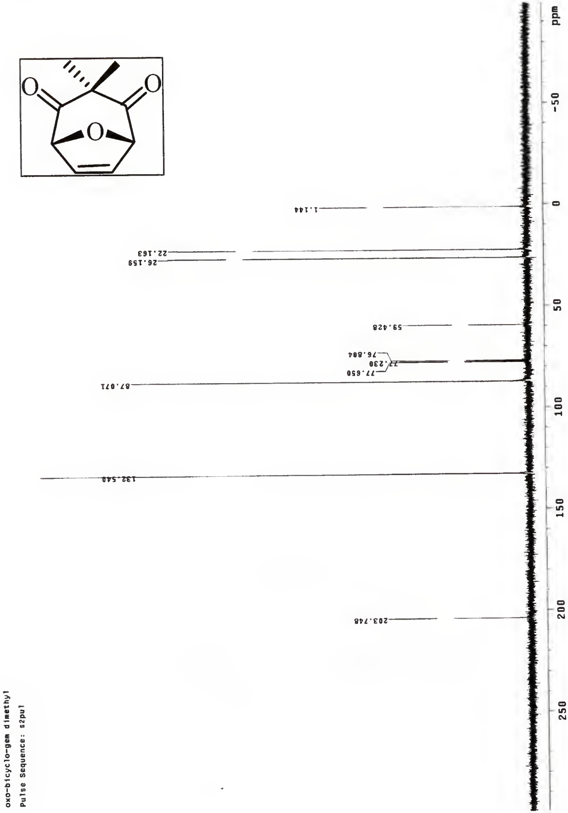
2.96
1.98
2.00
O
O
O



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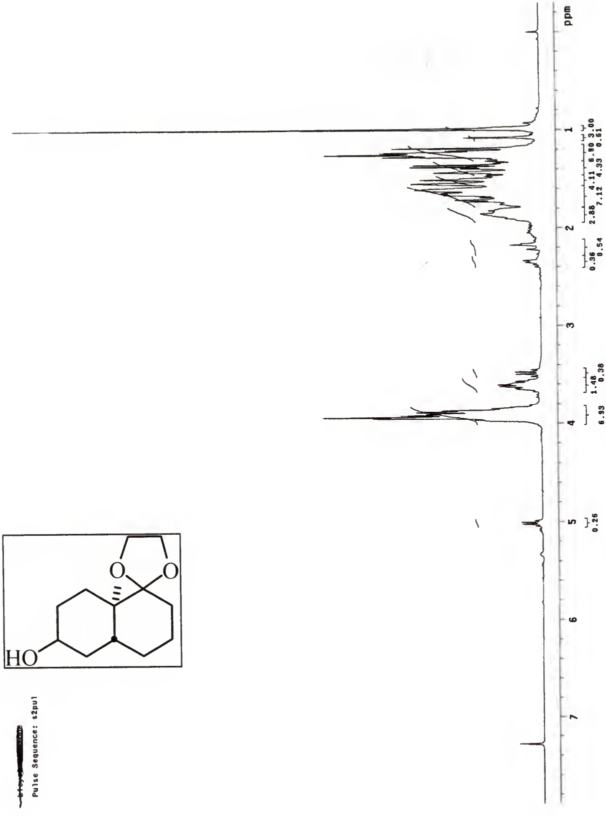
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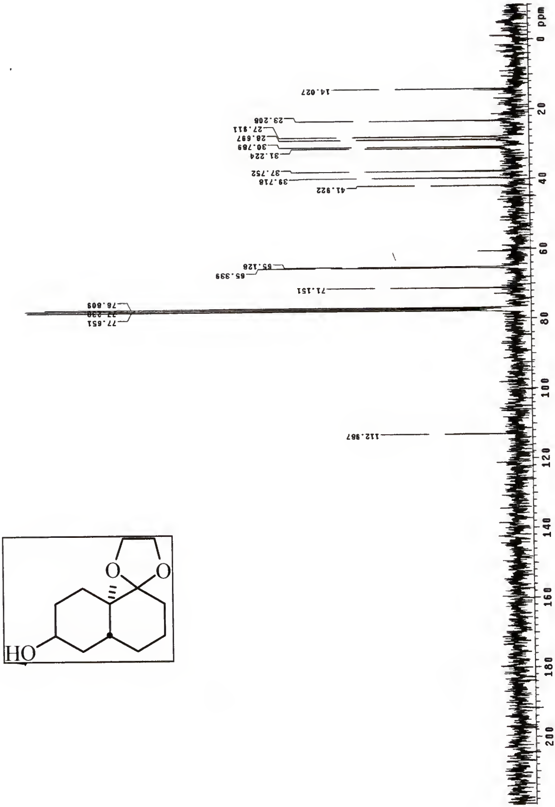
O
O
HO
Pulse Sequence: s2pul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76.809
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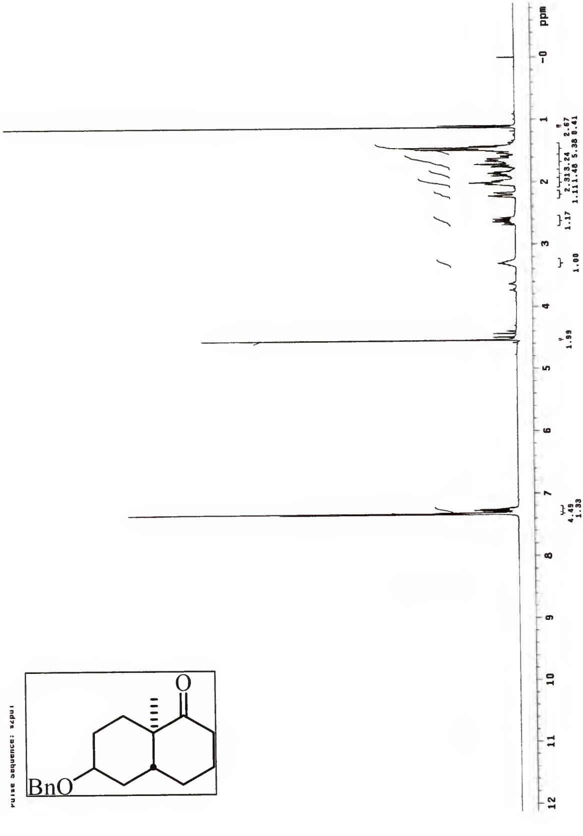
O
O
HO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O
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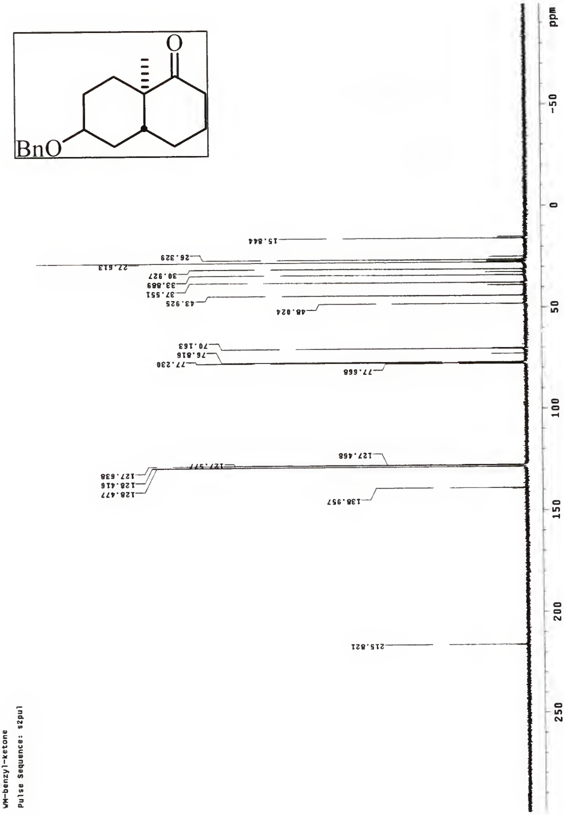
1.33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76.816
77.230
77.668
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127.577
127.638
128.416
128.477
138.957
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50
100
150
200
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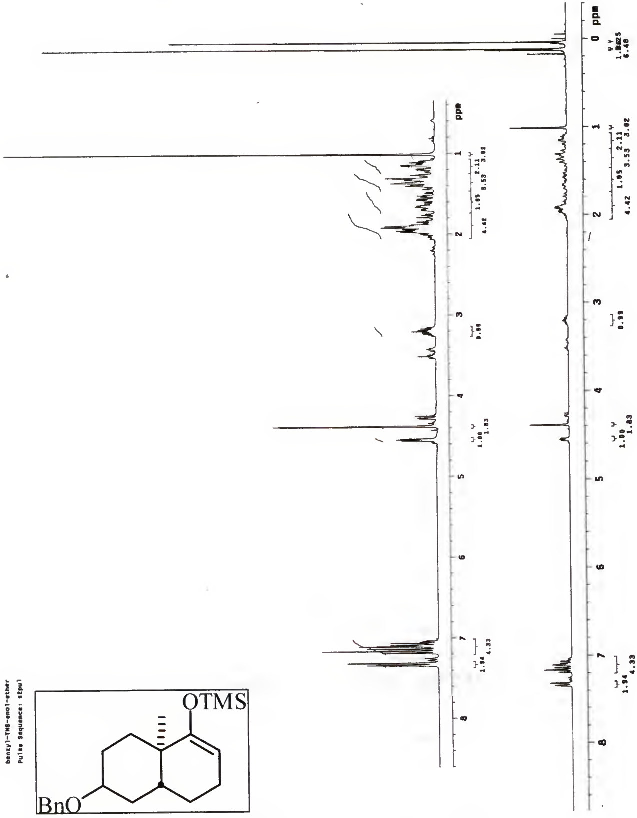
benzyl-TMS-enol-ether
Pulse Sequence: s2pul
OTMS
BnO
ppm
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2
3
4
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6
7
8
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1.83
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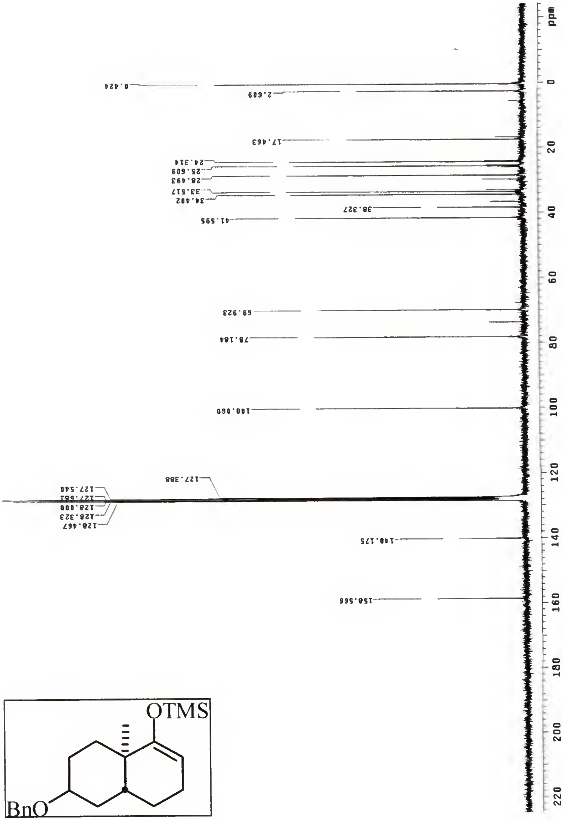
4.33



standard C13 parameters
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BIOGRAPHICAL SKETCH

William Allen Batson a. k. a. Buck was born in Clarksdale, Mississippi in 1976 and grew up in Jacksonville, Florida. Growing up in the south, sports were the center of his life, especially football, and his interest in science would not be realized until he attended high school. Buck graduated from Middleburg High School in 1994 where he excelled not only in his classes where he finished in the top 10% in his class but also in sports. He was involved in football, soccer and track. Out of all the sports he played none was more important to him than football. He set a record his senior season for the most tackles in a season and received the coaches' award for his dependability and leadership. It was because of his involvement in sports that sparked his interest in attending college. He was offered a partial football scholarship to attend Greenville College in Greenville, Illinois. Upon his arrival he enrolled in the pre-med program but his main focus was on athletics. This all changed when he took organic chemistry and met Dr. Daryl Cox. Dr. Cox was responsible for seeing the potential that Buck had and that he was just letting it slide by from not taking his education seriously. Dr. Cox was a tremendous factor in Buck's life and opened his eyes to the wonderful world of chemistry. From this experience he changed his course of study toward completing a dual major in chemistry and biology. This experience not only affected his studies but also his role as a leader for his football team. His senior year he was elected team captain and led his team in tackles and was voted MVP. He also received notice as a NCAA Division III Honorable Mention All-American Upon completing his undergraduate studies he was offered the opportunity to play professional football in Europe but interest in chemistry superseded and he choose to attend graduate school at the University of Florida to study organic chemistry. He began his journey by joining Dr. Eric Enholm's group and he worked in that group for two years before deciding that he wanted to do natural product synthesis. He then left Eric's group and joined Dr. Dennis Wright's group where he is finishing his graduate studies. Right now he is wrapping up his doctoral degree and is looking forward to starting his post-doctoral fellowship with Dr. Marcus Tius at the University of Hawaii with the goal of eventually pursuing a career in industry.